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THE ACCURATE CLINICAL STUDY OF BLOOD-SUGAR.

By Solomon Strouse, M. D., Chicago,

assisted by

Irving F. Stein, M. D., and Alan Wiseley, M. D.

(From the Department of Medicine, the Michael Reese Hospital and the Morris Institute for Medical Research.)

The necessity of using large amounts of blood and the inherent technical difficulties of determining the sugar content have stood in the way of extensive blood-sugar determinations. It is true that many estimations of blood-sugar have been published, but most of these have come from different observers in different laboratories, and with techniques not constant enough to permit of comparative criticism. Yet as the study of the normal and pathological in carbohydrate metabolism progresses, the need of methods allowing many determinations on the same person and not requiring the services of a specially trained chemist has been felt.

Ivar Bang[1] was perhaps the first to attempt to fill this need with a method meeting the requirements of the clinic and the demands of scientific accuracy. In this method only a few drops of blood are used, and the technique, once acquired, can be performed by any clinician capable of performing the usual clinical laboratory routine. Since the publication of the original article, many workers have used the method, and Fitz[2] in this country has made an elaborate comparison of it with the Bertrand method. We did a considerable amount of work with the Bang technique, and feel that the procedure is extremely valuable; but, for reasons which will be discussed later, all the work which forms the basis of this paper has been done in an entirely different way.

One of the difficulties of sugar determinations with small amounts of blood has been that the normal content is so small as to cause too large a percentage error. To obviate this difficulty Kowarsky[3] has suggested the use of a copper solution containing a known amount of dextrose. The technique devised by him is based on two accurate chemical procedures

(1) the Michaelis-Rona method of de-albumenizing blood; and (2) the Bertrand copper reduction method of determining sugar.

The simplicity and apparent accuracy of the technique described by Kowarsky appealed to us as worthy of investigation for use in several studies on carbohydrate metabolism; and after only a few preliminary observations it was evident that by this method clinical observations on blood-sugar could be made with an accuracy even beyond our expectations. The details, as described by Kowarsky, have been considerably modified as our work progressed, and the description given below is of the technique as now practiced in our laboratory:

SOLUTIONS.

I.	Copper sulphate (pure crystals)	8.0
	Dextrose (C. P.)	0.1
	Water to	200.0
II.	Pure Rochelle salts	40.0
	Sodium hydroxide (sticks)	30.0
	Water to	200.0
III.	Ferric sulphate	10.0
	Concentrated sulphuric acid	40.0
	Water to	200.0
IV.	Potassium permanganate	1.0
	Water to	200.0
V.	Liquor ferri oxidati dialysati (Merck)	5%
VI.	Sodium fluoride	0.2% solution

Also pulverized Rochelle salts.

Solution IV is used in a 10-fold dilution freshly prepared each day. It must first be standardized by titration against oxalic acid. The equivalent of the permanganate solution in copper is obtained by this titration. Kowarsky recommends the following technique of standardization. Exactly 0.1 gm. of ammonium oxalate is dissolved in 100 cc. of distilled water. To 10 cc. of this solution 2 cc. of concentrated sulphuric acid are added. The diluted permanganate solution is now titrated against this oxalic solution to a permanent red reaction. The number of cubic centimeters of permanganate solution is then made the denominator of a fraction of which the constant 8.95 is the numerator. The resulting figure equals the amount of copper in milligrams represented by 1 cc. of the permanganate solution.

APPARATUS NEEDED.

1. Several centrifuge tubes of ordinary laboratory size carefully calibrated and marked at the 0.5, 1.0, 5.0 and 10.0 cc. points. We have found it advisable to calibrate our own tubes, as several supposedly accurate tubes showed errors as high as 40 per cent.
2. An ordinary laboratory centrifuge.
3. Small Erlenmeyer flasks—capacity 50 cc.
4. An Allihn filter and suction pump.
5. Washed asbestos.
6. Burette of 10 cc. capacity divided into 1/20 cc. (0.05).
7. Volumetric flasks, 2, 3 and 5 cc. pipettes, etc., as found in any laboratory.

THE METHOD.

The sodium fluoride solution is placed in one of the calibrated centrifuge tubes up to the 0.5 cc. mark. In practically all of our work the blood from a finger or ear prick was allowed to drop into the tube up to the 1 cc. mark, thus giving exactly 0.5 cc. blood. Water is then added up to the 5 cc. mark, a pinch of powdered Rochelle salts dropped in, the whole shaken and allowed to stand until the Rochelle salts are completely dissolved. Then the solution of dialyzed iron is added, making the total contents of the tube exactly 10 cc. It is now corked and vigorously shaken until the originally putty-like mixture becomes homogeneous and fluid. Centrifugalize for 3 to 5 minutes.

The dialyzed iron-blood mixture when removed from the centrifuge should show a water-clear supernatant fluid. Exactly 5 cc. of this clear fluid are used in the copper reduction, which is performed by mixing exactly 2 cc. of each of solutions I and II in the small Erlenmeyer flask and then adding the clear filtrate.

The reduction process must take place on an asbestos mesh over a *low constant* flame and must continue exactly 3 minutes from the time boiling starts. While this is going on, the asbestos filter is prepared and washed, and the suction pump thereby tested out. After 3 minutes boiling the Erlenmeyer is rapidly cooled under the cold water faucet *without shaking*, and the contents immediately poured on the filter. The reduced copper oxide remains in part adherent to the sides of the Erlenmeyer flask and to the surface of the asbestos filter, and both flask and filter must be carefully washed several times with distilled water.

The funnel is then disconnected from the filtrate flask containing the unreduced copper sulphate and the washings. The filtrate flask is thoroughly cleansed with distilled water and again connected up with the funnel. Three cubic centimeters of the acid ferric sulphate solution are now added to the original Erlenmeyer flask, care being taken that it is well distributed over the whole of the inside of the flask. The contents of the flask are then poured upon the asbestos in the funnel and allowed to stand 1 minute. By this time all the reduced copper will have been taken into solution, and the suction pump is again started. The Erlenmeyer flask is carefully washed 3 or 4 times with 3 to 5 cc. of distilled water, each washing being poured into the funnel of the suction pump. The contents of the filtrate flask are then titrated against the permanganate solution diluted 1:10, until a definite pink color persists.

The results are easily figured. The amount of permanganate solution in cubic centimeters is multiplied by the constant for this solution (as previously determined) and its equivalent in milligrams of dextrose obtained from the following table:

Copper.	Sugar.	Copper.	Sugar.	Copper.	Sugar.
1.95	1.0	3.50	1.8	5.00	2.6
2.15	1.1	3.70	1.9	5.20	2.7
2.35	1.2	3.85	2.0	5.40	2.8
2.55	1.3	4.05	2.1	5.60	2.9
2.75	1.4	4.25	2.2	5.75	3.0
2.90	1.5	4.45	2.3	5.95	3.1
3.10	1.6	4.65	2.4	6.15	3.2
3.30	1.7	4.80	2.5	6.35	3.3

But it must be remembered that 200 cc. of the original copper solution contained 100 mg. of dextrose, so that the 2 cc. used in the test contained 1 mg. of sugar. When this is subtracted from the sugar obtained, we have just the amount of sugar in the blood. Originally 0.5 cc. of blood was used, but only half the total (5 cc. filtrate) is used in the test, so that the amount of sugar represents that in 0.25 cc. of blood. From this it is easy to determine the amount in 100 cc. of blood, by multiplying by 400.

It is well here to call attention to the fact that for the titration to be successful the filtrate, after the addition of the dialyzed iron and centrifugalization, must be water clear. Two factors occasionally enter to prevent this. At times not enough Rochelle salts is added, and at other times there is insufficient iron. To obviate the latter possibility we have been in the habit of using 5 to 6 cc. of the iron solution. Students of the original Kowarsky article will note that he advises the use of "Merck's liquor ferri dialysati oxidati diluted with an equal amount of water." However, the liquor put out in this country is a 5 per cent solution, and must be used in its whole strength. Dilution according to Kowarsky's technique will spoil the test. At times the iron solution does not seem to maintain a constant strength, and often in the case of a new bottle it will be found necessary to use a little more or a little less than 5 cc.—always being careful, however, that the total equals 10 cc.

This whole procedure from beginning to end can be carried out in 15 minutes. Practically no special apparatus is required. The blood can be obtained in the hospital ward or the office, put in the tube with the fluoride solution and water and carried to the laboratory to be finished. Almost any physician (who knows the essentials of quantitative chemical analysis) after seeing the test performed a few times can carry it out himself. The chemical principles on which it is founded are sound and proved, and the only criticisms lie in its technical execution as outlined by us, and in the possible errors from the use of so small an amount of blood.

The measuring of the blood seems crude and inefficient, and we felt strong doubts as to whether the centrifuge tube method could possibly be accurate enough. Originally it was adopted temporarily by us in place of the "fläschenformige Röhrchen" of Kowarsky, which could not easily be obtained. Although we were decidedly of the opinion that the use of the tubes as described could not possibly give accurate results, a series of controlled experiments proved that our theoretical objections must fall before the proof of actual results. But even if others find this part of the technique inefficient, it can offer no logical objection to the value of the method. Certainly a more scientific procedure would be the weighing of the centrifuge tube just before and just after the blood has been placed therein.

The method of de-albumenizing the blood has received so much study and has met with the approval of so many chemists that we need not further discuss it here. Likewise the Bertrand sugar titration has met with general approval. As a matter of fact the control tests of the copper-dextrose solution, made constantly in the course of the work, gave convincing evidence that all the sugar in solution was quantitatively recovered by this technique.

Many statements have been made as to the impossibility of obtaining accurate results in any method in which less than 5 or 10 cc. of blood are employed; but on the whole these objections have come from men who have not tried to determine blood-sugar with small amounts of blood. Bang and his followers are convinced of the accuracy of the new Bang micro-method, in which only a few drops of blood are used, and a critical study of the brilliant results already published by the use of his technique fails to reveal anything less scientific than those published by workers using larger amounts of blood. On the other hand, methods such as Bang's or the one here described open up fields of scientific investigation absolutely impossible where large amounts of blood are necessary. The effect of withdrawing blood on the subsequent determinations of blood-sugar, the effect of the excitement of more than one venopuncture have been proved beyond a doubt for laboratory animals; and surely the emotional instability of sick patients is a factor which must be considered.

No better illustration of the need of a "clinical" method can be cited than the obscurity surrounding the definition of normal blood-sugar. One finds in the literature figures varying from 0.04 to 0.12 per cent, but, until Jacobson[4] studied the subject by serial determinations on single individuals with special reference to the effect of diet and of ordinary physiological stimuli, the significance of these limits was not apparent. Furthermore, in the field of carbohydrate metabolism and especially in the obscure interrelations between glycemia and glycosuria, it has been definitely shown that animal experiments cannot be translated into human physiology and pathology; and this fact adds further reason to the need of investigating methods that simplify the study in man.

It has seemed to us that the method we have described fills all the requirements of an absolute science as well as those of the clinic, and is therefore an ideal method for the pursuit of extensive investigations of the numerous problems of blood-sugar. When compared with Bang's micro-method, it is seen that it requires more blood, but in this respect only does it compare unfavorably. The final titration with the Bang method, in which a purple blue must be differentiated from a green blue has, in our hands, at least, proved a much more difficult problem than the simple end-point in permanganate titration. Also the necessity of working in an atmosphere of carbon dioxide complicates the Bang technique, and the addition of a known amount of sugar in Kowarsky's method makes the percentage error less.

THE NORMAL BLOOD-SUGAR.

The first problem investigated by us was one which seemed of fundamental importance and without which any subsequent studies would be futile, viz., the problem of normal blood-

sugar and its variations under normal conditions. We quote some of the published figures for normal blood-sugar in man:

Author.	Percentage.	Method.	Number of determinations.
Naunyn [5]	0.07 -0.10	Abeles.	4
Klemperer [6]	0.08 -0.11	.....	..
Liefman & Stern [7]	0.07 -0.11	Knapp.	20
Hollinger [8]	0.07 -0.10	Knapp.	10
Bang, *l. c.*	0.10 -0.11	Micro-method.	3
Leire [9]	0.06 -0.11	Micro-method.	17
Frank [10]	0.08 -0.11	Bertrand.	15
Oppermann and Rolly [11]	0.062-0.088	Bertrand.	15
Kowarsky, *l. c.*	0.05 -0.11	Kowarsky.	20
Freund and Marchand [12]	0.055-0.12	Frank.	20
Purjesz [13]	0.045-0.087	Bertrand.	10
Jacobson, *l. c.*	0.09 -0.116	Micro-method.	14

It will be seen from the above statistics that there are wide variations in the amount of sugar as found by different workers with different methods. Some of the authors give details as to the conditions under which the determinations were made, but most of the "normals" are indefinite. Furthermore, the different techniques and the varying amount of blood used in individual series would make comparisons unprofitable, so that on the whole it seems difficult to explain the variations. The likely causes would be the varying conditions of the experiments, the fact that in one series the studies were made on a fasting stomach and in another after a meal, that the effect of diet, of exercise, of other diurnal variations in any human being which influence sugar mobilization, was not considered. It seems almost a foregone conclusion that a carbohydrate-rich diet should, even in a normal being, influence the amount of circulating sugar and that the diet factor must be considered in any study of the normal. Yet Tachau [14] claims that in 15 normals who were given 100 gms. of dextrose on an empty stomach the blood-sugar was no higher one hour after the ingestion of the sugar than before. However, he failed to make determinations on each individual before the dextrose was given and, as we shall show later, such determinations are necessary if one is to interpret results correctly. He also made no determinations before the end of an hour, whereas Jacobson claims that a hyperglycemia ensues within half an hour after the feeding of dextrose to normal persons.

Jacobson also showed conclusively that after an ordinary meal the sugar content of the blood reached a higher point than before the meal, and that this rise was due entirely to the carbohydrate content of the food. In 15 persons receiving 100 gms. of dextrose on an empty stomach before breakfast he invariably found a hyperglycemia usually within half an hour after ingestion, while of 14 persons receiving 167 gms. of bread, all reacted with hyperglycemia and 6 with glycosuria. The only difference between the effect of dextrose and of starch was in the rapidity of the rise and fall of the sugar curve, undoubtedly due to the differences in the rate of absorption. Protein and fat had no such effect, and the giving of fat with the starch produced a milder hyperglycemia than that produced by the starch alone. Leire also claims to have found a rise in blood-sugar after an ordinary meal.

In order that we might have a clearer understanding of the actual meaning of the word "normal" as applied to blood-sugar, we planned experiments in which the same individual should be the subject of studies under varying conditions of an active normal life. Perfectly healthy young men and women were used and we planned to plot the normal curve, beginning early in the morning just after rising, after breakfast, and before and after dinner. All post-prandial determinations were made one hour after eating, and in several cases the studies were repeated on the same person either the next day or in a few days after the original work. Obviously such a scheme can be followed only when small amounts of blood are used.

It was soon found that a very definite curve could be plotted for every individual and that, although the exact height of the figures varied slightly under similar living conditions, the curves of all normal individuals followed similar lines. It was also evident that the most important factor influencing the daily changes in blood-sugar was the carbohydrate in the diet. The lowest normals were usually obtained in the early morning; after breakfast there was a rise followed by a fall and a second rise after dinner. In persons who took no carbohydrate such a curve was not followed, and practically the same figure was obtained all day. In many instances, when we received the blood marked in such a way as to make it impossible to know its source, we were able to state that the person had eaten no starches; and in this way an interesting control over the accuracy of the method was accidentally developed. All experiments were carried out in the same manner. Each day's work was planned in advance, the assistants procured the blood and gave the specimens to the writer for the actual sugar determinations, which were thus carried out in an entirely objective manner. Occasionally, instead of taking the ordinary mixed diet the subject would go on a protein-fat régime, and in every instance the writer could diagnose the "mistake."

The work on the normal individual was supplemented by work on diabetes (about 25 determinations) and on miscellaneous hospital patients (also about 25 determinations). But as these titrations will form the subject of subsequent communications they will be mentioned in this report only when needed to force comparisons.

TABLE I.

Time.	Min.	Max.	No. determ.	Average.
Before breakfast	0.04	0.088	6	0.066
After breakfast, 1 hr.	0.08	0.124	5	0.103
Before dinner	0.04	0.096	15	0.066
After dinner, 1 hr.	0.068	0.140	35	0.091
Totals	0.04	0.140	61	0.084

These figures are collected to give a general view of blood-sugar variations. Of more importance it seems to us are the individual variations. Some of these are shown in the following table:

TABLE II.

Patient.	Before breakfast.	After breakfast.	Before dinner.	After dinner.
I.	0.04	0.124	0.084	0.092
II.	0.088	0.140	0.088	0.104
III.	0.052	0.08	0.096	0.104
IV.		0.092	0.04	0.076
V.		0.08	0.06	0.08

This table shows quite definitely that there is not a fixed value for the "normal" blood-sugar; and that the "normal" varies for each individual, depending on the diet. The variations are between rather wide limits and to obtain any true idea of the behavior of an individual toward sugar transportation, it is necessary to determine the sugar before and after an ordinary meal. The only difference in blood-sugar between the normal and the diabetic organism is one of degree. The diabetic curve is identical with the normal curve, but the low figures are not obtained and the variations are higher. On the other hand, in mild diabetes the blood-sugar on a fasting stomach may be within normal limits. Therefore, comparisons of single blood-sugar determinations on individuals, either from the standpoint of diagnosis or of treatment, are without value.

One most interesting case will illustrate the necessity of determining the curve of blood-sugar. A young man had for about 30 days multiple furuncles which despite active surgical intervention refused to heal. Physical examination showed a very healthy man with no cause for the persistence of the furuncles. The urine examination for several days showed the following: 24 hour specimen, amount 2500 cc.; s. g. 1012, no albumin, no sugar; microsc. exam., negative; certainly not the kind of urine to make one suspect a disturbance of carbohydrate metabolism. Nevertheless because the persistence of the furunculosis suggested the behavior of a diabetic and because the patient's mother had died of diabetes, we thought it worth while to study his blood-sugar curve. On two days the tests were made and the curve was plotted with the patient on the same diet as was used in our normal determinations. The blood-sugar in the early morning on an empty stomach was 0.06 per cent; 1 hour after breakfast 0.14 per cent, 1 hour after dinner 0.168 per cent; showing a definite alimentary hyperglycemia. Dr. Eisendrath, the surgeon asked us to assume charge of the case, and a strict carbohydrate-free diet was ordered. In 24 hours the furuncles then present had begun to heal; within 48 hours no new ones had developed and by the end of a few days all the old ones were healed. In this case the test, as applied by us, was of distinct therapeutic value, whereas had we done only a single examination without relation to diet we might have missed the post-prandial hyperglycemia. Incidentally, such a case with a diabetic family history and also with urine suggestive of chronic nephritis induces speculation on two interesting scientific problems (1) the early changes in diabetes mellitus and (2) the interrelations between glycemia and glycosuria. In the study of both of these problems the basic facts on normal blood-sugar here laid out and the technique here described have already been employed.

CONCLUSIONS.

1. The Kowarsky method of determining blood-sugar, as modified by us, affords an efficient and accurate means of studying blood-sugar in man.

2. The normal blood-sugar, as shown by a study of 61 determinations, varies from 0.04 per cent to 0.12 per cent (in one instance 0.14 per cent) with an average of 0.084 per cent.

3. These variations are due to the varying factors in the ordinary day of any normal individual—especially to the diet factor.

4. Carbohydrate in the diet raises the blood-sugar.

5. The blood-sugar of a normal man describes a curve reaching its lowest limits before breakfast and before dinner, and invariably showing a rise one hour after meals.

6. Blood-sugar determinations to be of any value must be performed before and after an ordinary meal containing carbohydrate.

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CHORIO-EPITHELIOMA OF THE TESTICLE.*

By JEAN V. COOKE, M. D.

(From the Pathological Laboratory of the University of California Hospital, San Francisco.)

Teratomatous growths of the testicle include certain tumors which closely resemble chorio-epithelioma in women. In 1878 the first of these was described by Mallassez and Monod and designated a *sarcome angioplastique*, but Schalgenhaufer in 1902, noting the similarity between these tumors and chorio-epitheliomata of trophoblastic origin, first expressed the view that both were in reality identical. Wlassow in the same year also noted the similarity between these two neoplasms, but apparently attached no importance to it. Subsequently, cases of chorio-epithelioma of the testicle have been recognized from time to time and at present 46 instances have been recorded. Some of these tumors have been the subject of detailed study and discussion; others have been reported briefly and with

* The case here reported was observed and the autopsy performed at the Pennsylvania Hospital, Philadelphia.

fragmentary clinical and pathological notes. A few cases are reported in a too incomplete form to be of value. To these cases collected from the literature I wish to add another and also to call attention to several features apparent upon study of the material now at hand.

Our patient was admitted at the Pennsylvania Hospital (Hosp. No. 826) to the service of Dr. J. C. Wilson, to whom I am indebted for the clinical notes.

T. S., an Irishman 26 years of age, a worker in a salt factory, was admitted on June 6, 1911, in a semi-stuporous condition. His family and past history were negative. The history of the present illness, obtained from a relative, follows: Five days before admission the patient returned from work complaining of severe cramp-like abdominal pain. Several times during that evening he vomited a brownish-red material, and two days later again vomited similar material. He had severe headache continuously, had been rather stupid, and his eyesight had become poor. At times the abdominal pain appeared to be more severe in the epigastrium, but as a rule it was general and not localized. His appetite was poor.

Physical examination.—A large, well-built, well-nourished man, who lies in a semi-stuporous condition, and answers questions slowly and unintelligently. The eyelids are closed most of the time, but at intervals he appears quite uncomfortable and groans. The tongue is protruded in the mid-line and is not tremulous. The teeth are in good condition and the fauces are not congested. The chest is large and well formed. The mammary glands are rather prominent, the left nipple is enlarged and is surrounded by a fairly well-developed glandular base. Pressure upon the breasts expresses a few drops of colostrum-like fluid. The heart and lungs are negative except for a small area of impaired resonance in the left axillary region. Here the breath sounds are roughened. The abdomen is full and soft, but not distended; there is slight, general tenderness on palpation, but no muscle rigidity. The liver and spleen are not enlarged. The scrotum is occupied by a large firm ovoid tumor of the right testicle which is round, tense, dull to percussion and does not transmit light. The extremities are well developed and normal. The patellar reflexes are not obtained. The pulse is of good volume and moderate tension, regular in rate and rhythm; the vessel-wall is soft. The urine has a specific gravity of 1033, is reddish brown and slightly turbid, acid, contains no albumin or sugar and on microscopic examinatien is negative. Wassermann reaction negative. Temperature, 99° F.

Progress.—For two days after admission the patient's condition remained unchanged. On the third day he became more restless and noisy and groaned frequently. During the night he had three dark, tarry bowel movements. He seemed very uncomfortable and apparently had pain in his head and abdomen. About 12 hours later he vomited approximately 1000 cc. of blood which was partially clotted.

During the following night he was restless and the next morning vomited a small quantity of blood clots, but no fresh blood. Again he complained of pain in his head and abdomen. During the day he passed by the bowel a small amount of changed blood. The leucocytes were 25,000 with 70 per cent of polymorphonuclears. A blood culture was sterile. The following day (the fifth after admission) his condition remained practically unchanged, except that the temperature rose several degrees. In the evening he died. The underlying pathological condition was not suspected, and the clinical diagnosis was "gastric hemorrhage."

Autopsy, June 12, 1911 (A 1441): 11 hours after death.

Anatomical diagnosis. Chorio-epithelioma of right testis with metastases to brain, liver, kidneys, stomach, peritoneum and thyroid gland. Ulceration of metastatic nodule in gastric mucosa with extensive hemorrhage into the stomach and intestines. Cloudy swelling of heart, liver and kidneys. Acute splenic tumor. Hypertrophy of breasts.

The body is that of a large, well-nourished white man 178 cm. in length. The pupils are of moderate size and equal. No discharge from the ears, nose, or mouth. Both breasts are somewhat enlarged and a thin colostrum-like fluid can be expressed from the left nipple. There is a swelling of the right side of the scrotum measuring 7 x 7 x 11 cm. The extremities are not edematous.

The serous surfaces of the *peritoneal cavity* are covered with bloody fluid and there is a similar fluid in the flanks. In the pelvis there are probably 100 cc. of thick bloody fluid that has a purplish color. Attached to the upper portion of the sigmoid colon is an irregular mass, 2 cm. in diameter. Its surface is somewhat lobulated and dark red in appearance, with irregular areas of reddish grey. On section it is dark red and is traversed by an occasional greyish trabecula. The mass is attached to the sigmoid in two places by a band of connective tissue, 2 cm. in length. The omentum shows small lobules of fat and in places is quite dark in color. The appendix is normal. The intestines are moderately filled with fluid and are somewhat discolored, but when the bloody fluid is wiped away, the serous surfaces appear smooth. The liver lies well behind the costal margin and the diaphragm reaches to the third rib on the right and the third interspace on the left. The gall-bladder appears normal.

Thorax.—On removal of the sternum the lungs collapse. The pleural surfaces are pale grey and everywhere free from adhesions. On the anterior surface of the lungs there are some small raised firm areas which are slightly darker than the surrounding pulmonic tissue. The pericardial surfaces are smooth and glistening and the cavity does not contain any excess of fluid. The *heart* weighs 310 grams and measures 12 x 9 x 5 cm. The pericardial surface is smooth and there is a considerable amount of subepicardial fat. The organ shows no gross abnormalities. The coronary arteries are delicate and patulous. The *right lung* weighs 460 grams. It is small, collapsed, and pale grey in color. The pleural surface is smooth and glistening. Beneath the pleura and through the pulmonary substance there are scattered rather firm spherical dark red nodules varying in size from 5 mm. to 15 mm. Section of these areas shows a dark red hemorrhagic tissue through which run irregular grey trabeculæ. Some of the small nodules on section show smooth reddish-grey cut surfaces and only a slight amount of hemorrhage, while the larger ones frequently reveal an irregular shaggy-walled central cavity containing hemorrhagic material. The lung is dry and pale. The pulmonary artery contains elastic post-mortem clots and appears normal. The bronchial lymph nodes are small.

The *left lung* weighs 410 grams and is similar to the right. In addition to the small, dark red nodules scattered through the lung there is found on the diaphragmatic surface a large spherical nodule, 6 cm. in diameter, similar in appearance to the smaller tumors. The bronchi at the root, the bronchial lymph nodes and the pulmonary artery are similar to those of the opposite lung.

The *spleen* weighs 190 grams and measures 13 x 9 x 5 cm. The consistency is soft on section and the pulp is reddish purple in color. The Malpighian bodies are small. No tumor nodules are found. The *liver* weighs 1460 grams and measures 27 x 20 x 5 cm. The surface is smooth and reddish brown in color. Occasionally there are seen irregular dark red areas beneath the capsule. These areas measure from 3 to 10 mm. in diameter and are hemorrhagic. On section the liver is light brown and small nodules are found scattered through the liver parenchyma, similar to those noted beneath the capsule. The *gall-bladder* is of moderate size and contains some yellowish bile. The *kidneys* together weigh 280 grams. The right measures 11.5 x 6 x 4 cm. The capsule strips easily, leaving a pale brown surface. At the upper pole there is a small, dark red nodule, 5 mm. in diameter, similar

to those described in the other organs. The cortex is very pale, but the markings appear regular. The Malpighian bodies are just seen as minute points. The left kidney measures 13 x 5 x 4 cm. A nodule 1.5 cm. in diameter is found on the posterior portion of the kidney just below the hilum. This is dark red on section and similar to the areas noted elsewhere. Otherwise this kidney resembles its fellow. The *adrenals* are of moderate size. The cortex is very pale and opaque, otherwise they appear normal. The *urinary bladder* and *prostate* show nothing noteworthy.

The *left testis* measures 3 x 2 x 1.5 cm. and on section appears normal. The *right testis* measures 12 x 8 x 7 cm. and is rather firm in consistency. On section the tissue is for the most part hemorrhagic and necrotic. Some fairly large areas are seen which are dark red in color and friable. Through these grey linear streaks run irregularly. Other softened areas contain necrotic brownish material. No cysts are seen, nor are any areas found which are not dark red and hemorrhagic.

The *stomach* is moderately dilated and filled with dark reddish-brown material. In the fundus near the lesser curvature there is a nodule measuring 2.5 cm. in diameter, which is situated in the mucosa or submucosa and is freely movable. The surface of this nodule is quite irregular, dark red, and ulcerated. On section it appears exactly similar to the hemorrhagic metastatic nodules found in the other viscera. The mucosa around this is very slightly congested. The *pancreas* is firm and pale on section. It shows no gross lesions. The *duodenum* is pale and appears normal. In the *jejunum* and *ileum* there is a large amount of semi-fluid, bright red hemorrhagic material; while in the upper part of the intestines this material is of a bright red color, in the lower part of the ileum it is dark red. The lymphoid tissue is more prominent than usual. The *large intestine* contains dark greyish-black tarry material. When this is wiped off, the mucosa shows no gross lesions. Near the splenic flexure there is a large mass, measuring 15 x 7 x 6 cm., which is loosely attached to the serosa and does not involve the wall of the gut. It is covered by fat and connective tissue and on section is similar to the testicular tumor.

The *tongue, tonsils, pharynx, larynx, and trachea* are pale and show no gross lesions. The *thyroid gland* is of moderate size, firm, and on section is pale brown in color. The right lobe contains a dark red metastatic nodule, about 2 cm. in diameter.

The *brain* weighs 1400 grams. On removing the brain, the pia shows no excess of fluid. The cortex over the right median frontal convolution shows an irregular area of subpial suffusion of blood measuring about 2 x 3 cm. This is just in front of the anterior central convolution. The left occipital lobe at its posterior and lower portions is firmly adherent to the dura over an area about 5 cm. in diameter. On removing the brain, there is exposed in this portion a large, rather firm dark red mass, 6 cm. in diameter. On section this mass is exactly similar to those found in the various viscera. Section through the right frontal lobe shows beneath the area of subpial hemorrhage another metastasis 3 x 2 x 2 cm. This has involved the deeper portion of the cortex beneath the area described, but for the most part replaces the white matter. Sections of the remaining portion of the brain show nothing unusual.

Smears from bloody fluid in the peritoneum show neither pus cells nor bacteria.

Cultures from the heart's blood and spleen remain sterile.

Microscopic examination. Tumor of right testicle.—Sections were made through various portions of the growth and each block was studied, though one scarcely differed from another. By far the larger part of all the sections was occupied by areas of hemorrhage and fibrin, with here and there masses of pink-staining cells indefinitely outlined. Occasionally small masses of well-stained tumor cells were scattered through the structureless hemorrhagic tissue. At no point was there evidence of tubules, nor were any blood-vessels found.

Most of the sections, particularly those taken from the edges of the tumor mass, show areas where the tissues stain well, and the structure of the tumor can be distinctly seen. Large polygonal cells of the Langhans' type are massed about irregular blood spaces. Lining the blood spaces and separating them from the Langhans' cells are flattened multinucleated syncytial masses. The Langhans' cells vary somewhat in size and have an irregular polygonal shape, although frequently the cell outline is not clearly made out. The protoplasm is granular and shows a well-marked vacuolization which in some of the cells is so marked that the nucleus appears surrounded by a clear zone, outside of which the cell membrane is seen. The nuclei also show some variation in size and shape, but most of them are round, oval, or vesicular, and rather poor in chromatin. Each shows a distinct, fairly deep-staining nucleolus. Mitotic figures are common. There is no demonstrable intercellular substance, and no definite blood-vessel. Many parts of the tumor show multinucleated, rather basophilic, masses of protoplasm. Occasional giant cells of this character are found among the Langhans' cells, but their most common location is in sheets between the Langhans' cells and the large, irregular blood spaces which honeycomb the tumor, thus occupying the same position with relation to the Langhans' cells and the blood spaces that syncytium does in normal placenta.

The large blood spaces are filled with red corpuscles, fibrin and serum, with leucocytes scattered through the mass. No intercellular connective tissue can be demonstrated.

Tissue derived from the other embryonal layers is not found in any section of the tumor.

Sections through the metastatic nodules in the organs show the same type of tumor as the original growth. The smaller nodules show much less necrosis and the tumor elements are well preserved. Multinucleated syncytial tissue is found much more commonly and almost always lines the irregular blood spaces in flattened sheet-like masses. One section of kidney shows, near a fairly large metastasis, two medium-sized blood-vessels, in each of which lies tumor tissue surrounded by blood. These tongue-like tumors have evidently been continued through the lumina of the vessels from the larger metastatic mass and have been cut in cross section.

The *left testicle* appears normal and the tubules show well-marked spermatogenesis.

Heart.—The pericardium and muscle are normal.

Lungs.—The pleura is normal. For the most part the pulmonary alveoli contain air and appear normal, although occasionally patches of early broncho-pneumonia are seen. Sections of the dark red nodules noted in the gross description show metastases from the testicular tumor.

Spleen.—The Malpighian bodies appear normal, but are somewhat irregular. In the spleen pulp there are large numbers of polymorphonuclear leucocytes. There is no increase in the trabeculæ.

Liver.—The parenchymatous cells are swollen and granular. There is no increase in the portal connective tissue. Sections of the metastatic tumor nodules show the same appearance as described in similar nodules in the lung, except that the syncytial layer is more easily distinguished. At the edges of the nodule the tumor cells are invading the surrounding hepatic tissue.

Kidneys.—The epithelium of the convoluted tubules is somewhat granular and the cells are swollen. The glomeruli appear normal and there is no increase in interstitial tissue. A metastatic tumor nodule in the cortex shows the some appearance as that described elsewhere. The *adrenals* appear normal.

Thyroid gland.—The acini are fairly regular and contain colloid. The epithelium is flat. One section shows a large metastatic tumor nodule.

Left mammary gland.—The sections show masses of fat with an abundant fibrous connective tissue and fairly numerous tubules lined with epithelium. These are frequently isolated, but groups

of five or six are occasionally seen. Their size varies considerably, some being about the size of small non-lactating mammary acini and others larger—1.5 x 0.2 mm. Most of the ducts are somewhat irregular in outline and there is a tendency to an infolding of the epithelium. They are lined with a single layer of columnar epithelium, which shows a proliferation with an occasional mitotic figure near the basement membrane. In the lumen there are granular detritus, degenerating cells and cell shadows. Sections from the right breast unfortunately were not taken.

Alimentary canal.—Sections through the ulcerated nodule in the gastric mucosa show a considerable amount of necrotic and hemorrhagic tissue and some areas with typical chorio-epitheliomatous structure. No lesions are noted in the intestinal mucosa.

Brain.—The metastatic nodules are quite similar in structure to those found in the other organs.

The accompanying table shows the principal features of all the cases that have been reported.

The 47 cases below present a number of clinical features which may be summarized as follows:

The *age* of the patients varied from 16 to 46 years, but the large majority of cases occurred in individuals between 20 and 40 years old. Among the cases in which the side involved was mentioned, there was a slight predominance of involvement of the left testicle, the ratio being 6 to 5. In two cases an undescended testicle was the seat of the tumor.

The duration of the disease varied greatly. In most of the cases, it was less than a year; the longest was 2½ years and the shortest 2 months. Invariably the prognosis was grave. In 29 cases a fatal termination was specifically mentioned. One patient appeared to be well 5 months after operation. In the remaining 17 the post-operative result was not given.

The *local symptoms* consisted of testicular enlargement of

TABLE SHOWING COLLECTED CASES OF CHORIO-EPITHELIOMATA OF THE TESTICLE.

No.	Reporter.	Age.	Side.	Duration.	Result.	Other Teratomatous Growths in:		Remarks.
						Tumor.	Metastases.	
1	Mallassez & Monod.	27	Left.	1 yr.	Death.	None.	None.	Other teratomatous elements not looked for.
2	Carnot & Marie.	37	"	10 mos.	"	"	"	" " " "
3	Dopter.	28	Right.	6 mos.	"	"	"	" " " "
4	Wlassow.	....	....	.....	.....	"	"	No clinical data.
5	"	....	....	.....	.....	"	.....	" " "
6	"	....	....	.....	.....	Present.	.....	" " "
7	"	....	....	.....	.....	"	.....	" " "
8	Schlagenhaufer.	43	Left.	?	Death.	"	None.	
9	Breuss & Schlagenhaufer.	40	Right.	2½ mos.	"	"	"	Interpreted as hydatidiform mole.
10	Carey.	....	....	.....	.....	"	"	No clinical data.
11	Schmorl & Steinert.	22	Left.	.....	Death.	"	Present.	
12	Schmorl.	17	....	.....	.....	"	.....	
13	Steinhaus.	32	Left.	6 mos. +	.....	"	.....	
14	Risel.	20	"	.....	.....	.....	.....	
15	"	35	....	.....	Death.	.....	Present.	Original tumor not examined.
16	Emanuel.	26	Left.	4 mos.	"	Present.	.....	Atypical forms present.
17	v. Hansemann.	28	Right.	.....	.....	.....	Present.	Original tumor not examined.
18	Askanazy.	24	Right.	1 yr.	Death.	None.	.....	Atypical forms present.
19	Scott & Longcope.	45	"	2 mos. +	"	"	None.	Tumor of undescended testicle.
20	Dillman.	32	Left.	4 mos. +	"	Present.	"	
21	Frank.	40	?	2 yrs.	?	None.	.....	
22	"	16	Left.	2 mos. +	?	Present.	.....	Atypical forms present.
23	Sternberg.	26	Right.	1 yr., 2 mos.	Death.	None.	None.	
24	Chevassu.	30	Left.	3 mos.	?	"	.....	
25	Lawrence.	....	....	.....	.....	Present.	.....	
26	Reinhold.	30	Right.	7 mos.	Well?	"	.....	Well 5 mos. after operation.
27	Bernstein.	34	Left.	4 mos.	Death.	None.	None.	
28	"	29	Right.	.....	"	"	"	
29	Bonney.	....	....	.....	.....	"	.....	
30	"	....	....	.....	.....	Present.	None.	
31	Orton.	38	Left.	5 mos.	Death.	None.	"	
32	Mönckeberg.	19	"	10 mos.	"	"	"	
33	"	34	Right.	.....	?	"	.....	
34	"	Young.	....	.....	Death.	Present.	None.	
35	Chuvin.	20	Right.	6 mos.	"	None.	"	
36	Taylor.	28	Left.	8½ mos.	"	Present.	"	
37	Fink.	35	....	.....	"	None.	.....	
38	Gruner.	25	Left.	5 mos. +	?	Present.	.....	
39	Glaserfeld.	23	"	2½ yrs.	Death.	"	None.	
40	Sigl.	34	Right?	6½ mos.	"	None.	"	Several congenital abnormalities.
41	Conforti.	46	Left.	2½ yrs.	"	"	"	
42	Zenoni.	32	Right.	.....	"	"	"	
43	Marcora.	29	Left.	1 yr.	"	Present.	.....	
44	Keenan.	20	Right.	7½ mos.	"	None.	None.	Tumor involved only the epididymis.
45	Tirumurti.	35	"	2 mos.	"	"	"	Tumor of undescended testicle.
46	Warthin.	35	"	.....	"	Present.	"	Hyperplasia of breast.
47	Cooke.	26	"	?	"	None.	"	" " "

varying degree unaccompanied by discomfort, or at most by dull dragging pain. As would be expected, the general symptoms varied with the localization of the metastatic tumors. By far the most common were referable to the secondary pulmonary growths, viz., hemoptysis and dyspnœa. A common finding was enlarged abdominal lymph nodes, which could be palpated and in some cases caused pressure symptoms. In several cases fatal hemorrhage occurred from metastases in the lungs, stomach or intestines. In two cases hypertrophy of the breasts with secretion of colostrum-like fluid was observed, but in none of the others was reference made to the condition of the breasts. Cachexia with loss of weight and strength was remarked in the terminal stage of all the cases.

Obviously, chorio-epithelioma of the testicle has no distinctive clinical feature and differs very slightly from other malignant testicular growths, except that occasionally it has been accompanied by hyperplasia of the breasts. Metastases become disseminated early and usually the patient is beyond hope when a physician is consulted.

Typically in their chorio-epitheliomatous portions the tumors are very hemorrhagic and necrotic. Microscopically the living tissue is composed of large, faintly staining polygonal cells of the Langhans' type and, among these, multinucleated islands of syncytium are scattered. Numerous irregular blood spaces, frequently lined with flattened syncytial plates, are distributed through the Langhans' cells. On the other hand, in a few instances the chorio-epithelioma has consisted of isolated cells or groups of cells which stain more deeply and are very irregular; occasionally, no multinucleated masses are present. Three cases have shown the type of growth first mentioned, in some part of the tumor, while in other parts the cells and arrangement have presented variations of an exceptional nature. For example, besides the usual alveolar arrangement, the Langhans' cells are found in a more independent proliferation consisting of duct-like and complex papillary forms lining cystic spaces.

In addition to the chorio-epitheliomatous portions, teratomatous or teratoblastomatous elements have been found in the original tumor in about half the cases and, in three, other structures beside the chorio-epithelioma have been found in metastases, although the latter have not shown malignant characteristics. Therefore, it seems scarcely open to doubt that these tumors are derived from pluripotential cells. While derivatives from more than one embryonal layer have not been found invariably, this may be due to the fact that they were present in such small amount that serial sections would have been necessary to demonstrate them; or, as seems more probable, the malignant chorio-epitheliomatous tissue may have invaded and destroyed the other elements just as in most cases it has destroyed the testicular tubules.

Perhaps the most interesting feature of the case I have reported is the hyperplasia of the breast with the secretion of a colostrum-like fluid—a phenomenon which Warthin also has observed. In Warthin's case, after the surgeon had removed the testicular tumor, the breast decreased in size, but later, during the development of general metastases, the hyperplasia became more marked than it had ever been. Unfortunately, in no other case has a note been made regarding the condition of the breasts.

At present the more plausible theories of mammary secretion ascribe the activation of the glands to a substance (hormone?) originating from one or more of the three sources—the embryo, the corpus luteum, and the placenta. There is evidence in favor of each view, but none rests on a firm basis. In the cases observed by Warthin and myself the association of functional activity of the breast, with a placenta-like tumor present in the body, suggests that a substance may occur in chorio-epitheliomata and probably also in the normal placenta which activates the mammary glands.

The precise nature of these testicular growths has been disputed and the opinions expressed regarding their origin have varied widely. It has been difficult to account satisfactorily for teratomatous and teratoblastomatous testicular tumors which contain trophoblastic elements. The three possibilities which immediately suggest themselves are that they arise (1) from the interstitial cells of the testicle; (2) from misplaced multipotential cells included in the organ during embryonic development; or (3) from the spermatogenic cells themselves.

A few observers have favored the endothelial origin of these tumors. Early French writers (Mallassez and Monod, Carnot and Marie, Dopter) believed they were sarcomatous and attributed vaso-formative properties to them. A similar view has also been expressed more recently by Sternberg, who thinks the multinucleated masses in the tumors are endothelial and that the coincidence of these "endothelial sarcomata" with teratomatous tissue is merely accidental. But this view has not been generally accepted.

Mönckeberg concluded that the elements resembling syncytial masses found in these tumors are not always the same, and divided the tumors into two groups: (1) those with chorio-ectodermal formations and syncytial epithelium—and to these he would add teratoid tumors in which the syncytium is similar but not of epithelial origin; (2) simple or teratoid tumors with perivascular lymphangio-endotheliomatous formations and syncytial protoplasmic masses with an endothelial origin. Conforti also thinks this tumor is neither ectodermal in origin nor related to teratomata, but that it is derived from capillary vessels and, therefore, a perithelioma. According to this writer, the multinucleated masses are giant cells formed in response to a chemical stimulus from the necrotic tissue of the tumor, and are similar to the giant cells formed around a foreign body.

Most writers, however, have considered that the portions of these growths which resemble chorio-epitheliomata are epithelial, although their views differ regarding the nature and origin of the tissue resembling trophoblast. A majority of the observers agree that the tumors should be considered teratomatous with actively proliferating malignant portions indistinguishable from true chorio-epitheliomatous tumors.

In general, therefore, the theories of origin of teratoma have been utilized to explain the genesis of these tumors, but

the nature of the malignant chorio-epithelioma tous tumor has been the subject of a number of hypotheses. The views expressed have chiefly dealt with the question of "specificity," *i. e.*, the question of identity of these tumors in men and of morphologically similar tumors in women. Schlagenhaufer, taking the view that teratomata originated from a fertilized polar body, advanced the hypothesis that chorio-epithelioma of the testicle arose from elements in the fetal membranes formed during the development of the tumor. He believed that its genesis is quite analagous to chorio-epithelioma in the female, and that it arises from specific chorionic epithelium. This opinion is based chiefly upon the re-examination of a case reported by Breuss which Schlagenhaufer interpreted as an hydatidiform mole. Such a degeneration, Schlagenhaufer affirmed, was known to occur only in tissue of trophoblastic origin and its presence indicated a similar origin for these tumors. Nevertheless, he has failed to convince others that the tumor in question was really an hydatidiform mole; and his view that these testicular tumors arise from a fertilized polar body is an hypothesis which has not found wide support.

Most writers hold that chorio-epithelioma of the testicle originates from a dislocated blastomere and likewise the same theory at present has a considerable vogue in explaining the origin of teratoma. During the early stages of segmentation of the ovum, displaced cells are supposed to lodge in the *Anlage* that forms the testicle and sooner or later begin to proliferate. However, it is not clear that such cells could form trophoblast, and Risel suggests that this phenomenon depends on the metaplasia of certain elements in the teratoma. He believes that the chorio-epitheliomatous tissue is merely a special form of embryonal epithelium arising from the epiblast and does not differ in its origin from other epithelial tissues. This view is based on a case in which a direct transition from definite neuro-epithelial cells of the teratoma to chorio-epitheliomatous masses was observed. In a case of ovarian chorio-epithelioma Pick has demonstrated a similar transition from neuro-epithelium to chorio-epitheliomatous cells, and regards his finding as a proof that an *Anlage* of fetal membranes is not necessary for the formation of the tumor.

On account of the teratomatous tissue found in the metastases a case reported by Steinert is of unusual interest. To account for this finding Steinert mentions three possibilities; (1) Multiple blastomeres deposited in the various organs during fetal life; (2) a primary testicular tumor composed of many blastomeres some of which later were carried to different organs; and (3) cells transported from the testicular growth which were derived from a misplaced blastomere and which were still at a sufficiently early stage to permit development of all three layers in the secondary tumors.

The origin of chorio-epitheliomata from the interstitial cells of Leydig seems quite improbable, though Nussbaum has stated that these are undeveloped germ cells.

The derivation of chorio-epitheliomata from the spermatogenic cells has received little attention, probably because such a conception would involve the much disputed question of parthenogenesis. In this connection a rather striking fact brought out by the study of the age of the patients in the reported cases may have some significance. Of the 38 cases in which the ages were given, 3 were under 20 and 5 were over 40, the youngest being 16 and the oldest 45 years of age; 16 cases occurred in the 3d decade, and 14 in the 4th. No cases before puberty have been recorded and none after sexual activity ceased. This strongly suggests that the development of the tumor is intimately associated with spermatogenesis. Furthermore, it seems rational to apply to these tumors the theory proposed by Adami to explain the origin of ovarian and testicular teratomata. This modified parthenogenic or germ-cell theory attributes the tumors to aberrant development of the spermatogonia or öogonia (or possibly their precursors) but not to the spermatozoa or ova themselves. It is known that certain cells—the germinal blastomeres, recognizable at an early stage of segmentation—are set apart and eventually carried to the generative glands where they later form ova or spermatozoa. All the intermediate stages of development between the primordial germinal blastomeres and the ova and spermatozoa retain the totipotential characteristics necessary for the formation of the three germinal layers of an embryo or an embryoma. Consequently a derivative from a germinal blastomere, normally present in the testicle, may take on aberrant characteristics and form a teratomatous or terablastomatous tumor, containing elements of fetal membranes. This hypothesis seems to meet all requirements.

It has been shown by Beard and other zoologists, who have followed the germinal blastomeres from the earliest stages of development, that certain of them may be dislocated and become included in other organs, for example, in the cranium, the gill-clefts or abdominal and thoracic cavities. From such dislocated cells may have arisen the chorio-epitheliomatous tumors described in the mediastinum by Ritchie and Frank, that in the omentum by Bonney and also in the cases noted by Boestrom and by M. Askanazy in which the original tumor was found in the brain. Similar growths originating in the ovary have been described by Lubarsch, Kleinhaus, Pick, Glinski, and Michel. Such an origin from a derivative of a germinal blastomere would explain the great predominance of the primary growths in the generative glands and it is noteworthy that the tumors have constantly developed during the period of active proliferation of the spermatogenic elements. Furthermore, it is of interest that Loeb, in the examination of the ovaries of 484 guinea-pigs, found structures resembling chorio-epithelioma 23 times. These were transitory tumors which were later converted into fibrous tissue. The growths were circumscribed and metastases were never formed. He attributed their origin to the parthenogenic development of ova, which developed only placental chorio-epitheliomatous tissue because of contact with the tissues of the host.

Indeed it is difficult to believe that the chorio-epitheliomatous portions of testicular tumors are not identical with the trophoblastic growths in the uterus. Morphologically the

two tumors are indistinguishable; they are of equal malignancy, they metastasize in a similar manner, both have a marked vaso-destructive action and both contain glycogen.

The recent demonstration by Abderhalden of a specific ferment (?) in the blood-serum of pregnant women may be of value in elucidating the disputed question of the specificity of these testicular tumors. When mixed with placental tissue, this ferment-like body in the serum has the property of liberating substances which give a test for amino-acids. If it should be found that the serum of patients with chorio-epithelioma of the testicle contains a similar substance acting upon placental tissue, this fact would strongly support the view that chorio-epithelioma of the testicle is a "specific" tumor and that it is genetically equivalent to chorio-epithelioma in women. Certainly this test should be made on the serum of all patients with these tumors. However, it must be remembered that a negative test would not exclude their trophoblastic origin. The commonly accepted view regarding these substances in the blood of pregnant women is that they are part of a protective mechanism against the spread of trophoblastic tissue. And, since cases of chorio-epithelioma show very little immunity against this tissue, the serum may possibly give a negative reaction.

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MITHRIDATIUM AND THERIAC, THE MOST FAMOUS REMEDIES OF OLD MEDICINE.[1]

By George W. Corner, M. D.,
Resident House Officer, The Johns Hopkins Hospital.

Of all the nations which at one time or another came to mortal conflict with Rome, none is now more utterly forgotten than the kingdom of Pontus. Her landmarks are uprooted, her temples are fallen, and of her mightiest ruler there remain but distorted legends. Mithridates the Sixth, surnamed Eupator, was the King Alfred of his day; or perhaps was more like Peter the Great, to whom Reinach the historian compares him. Between war and turmoil he found time to encourage at his capital all the arts and sciences. He spoke two and twenty languages, and conversed with subjects from all parts of his realm without need of interpreters. To him the famous Bithynian physician Asclepiades dedicated his works, and he himself dabbled in medical studies. It is certain that he was an enthusiastic experimenter with deadly poisons, and it is likely that his researches extended to the dosing of prisoners with fatal drugs. Tradition says that he carried out surgical operations upon his courtiers, and even poisoned some of his own family through excess of scientific zeal. Ever fearing treacherous attacks upon his life, and confident of his medical knowledge, he undertook to accustom his own body to harmful drugs by taking small daily doses of all sorts of poisons, both animal and vegetable, and finally compounded that strange pharmaceutical medley called after him Mithridatium, whose amazing history is briefly traced in this paper.

The story of Mithridates' death in the year 63 B. C. fires the imagination even at this day, and calls up lurid visions of Oriental strife. Routed at last by Lucullus and Pompey, the king escaped with two daughters (the queens of Egypt and Cyprus) and a few faithful followers to his castle at Pantikapaion on the Bosphorus, where he was besieged by his unfaithful son Pharnakes. His citadel in ruins and capture imminent, Mithridates drew from his jewelled sword-hilt a vial of poison and shared it with his daughters. The women expired at once, but the king, by a strange ironical fate, having hardened his body against poisons, was unharmed by the potion. Then, as the Roman soldiers burst into the palace, the king gave his last command, and fell upon the drawn sword of the last remaining member of his bodyguard.

Pompey had such superstitious regard for the memory of his enemy, that when a coffer was found in the citadel, full of manuscripts in the king's hand, recording his researches, the papers of the royal poisoner were given to the freedman Lenaeus to be translated. Thus the formula and composition of the Mithridatium were preserved, to be revered as a potent remedy for 1900 years. The works of Lenaeus were, of course, extant in the time of Pliny the Elder, who quotes from him a simple recipe for the drug: "Two dry walnuts, 20 leaves of rue, two figs, pounded and strewn with a little salt; taken fasting in the morning it should protect against every sort of poison during the day."

Whether or not this was the original composition of Mithridates, by the first century A. D. another and more complicated prescription was honored with his name. It was preserved in verse by Damocrates, an obscure physician, and is quoted in Galen's *De Antidotis* in a Latin poem of 30 verses.

The prescription is also given by Celsus (Lib. I, Cap. xxiii). But we do not have to search dusty pages of the ancients, for the same concoction extolled by Celsus and Galen in the first and second centuries is published with commendation in the English dispensatories of the eighteenth century.[2]

To decipher the nature of the ingredients, however, is a task of another sort. Different authors and editions give varying prescriptions, but the oldest existing formula is that of Celsus, which contains 33 ingredients, the nature of some of which we can only guess.

The chief of Nero's medical attendants was Andromachus the Elder, a man notable for skill in healing, upon whom first of Roman court physicians was bestowed the honorable title of Archiater. By this time the Mithridatium had come to hold a regular place in the doctor's armamentarium and perhaps it is not unduly fanciful to imagine the bloated features of Claudius Nero himself twisted awry over a nauseating dose of it. Andromachus undertook to improve the formula by adding new substances and, in order to protect his successors from error in compounding, put his prescription into 175 Greek iambic verses.

In the poem the physician dedicates his remedy to his sovereign, recommending it against poisons, serpent-bites, and the graver diseases, including blindness, incipient phthisis, dropsy, stricture, rabies, and so on. He then gives the formula and dosage. The additions made by Andromachus consist chiefly of squills, viper's flesh, and opium in generous quantities; he, too, mixed the ingredients in honey to make the drug more agreeable. The name *theriaca* is from the Greek word signifying wild or venomous beast, in token of the curative power of the medicine against the bites of animals. This is the prescription which held supreme honor as an antidote against all poisons, and as a remedy in all febrile diseases, until 1750 A. D. Under the name of Theriaca Andromachi, or Venice treacle, it is to be found in every work on the treatment of fevers for 1800 years.

What pharmacological conceptions led to the use of such mixtures is difficult to imagine. Most of the ingredients belong to those classes called by Paulus Aegineta desiccative

[1] Read before The Johns Hopkins Hospital Historical Club, January 11, 1915.

[2] See various editions of the London and Quincey's Dispensatories.

and heating, and should thus be useful against the supposedly cooling action of poisons and the acute infections. Many mediæval writers report that overdoses of theriac produce undue sweating and prostration. It is unnecessary to explain the addition of opium. The use of viper's-flesh forms a most interesting chapter of ancient medicine. Perhaps a clue to the old theories which led to its use is found in the *Royal Pharmacopœia* of Moses Charras (1678):

The powder of vipers is very much enlivened with the volatile salt wherewith the vipers abound, which enables it to force its virtues through the pores, though never so close shut, to the more remote parts of the body.

The viper's-flesh is, therefore, apparently the dynamic part of the composition, calculated to help the other ingredients permeate the body. In brief, the theriac of Andromachus was an opiated sudorific, a sort of glorified Dover's powder.

Both the Mithridatium and theriac found favor with Galen, who discourses of them extensively in his *De Antidotis*. In another treatise (*Galenus de theriaca ad Pisonem*) we are told that the noble Marcus Aurelius partook daily of the Mithridatium. Undoubtedly the great popularity and enduring fame of the two royal remedies, during all the Middle Ages, were largely due to the magical influence of the Father of Roman Medicine. No one remembered, or all ignored, the scornful words of Pliny (*Historia naturalis*, Lib. XXIX, Cap. 8):

The Mithridatic antidote is composed of four and fifty ingredients, none of which is used in exactly the same way, and the quantity prescribed is in some cases so small as the sixtieth part of one denarius! Which of the gods, pray, could have instructed man in such trickery as this, a height to which the mere subtlety of human invention could surely never have reached? It clearly must emanate from a vain ostentation of scientific skill, and must be set down as a monstrous system of puffing of the medical art.

The Saracen physicians, unlike their confrères the mathematicians and chemists, made little progress in learning. The shadow of Galen lay athwart the age, and the Moslems mistook it for a great light.

Under these circumstances it is natural that the theriac should be admired by the Arabians, and that in the interminable commentaries upon the Greek and Roman writings, which took the place of original work with them, they should discant at length upon its preparation and uses. Averrhoes and Haly Abbas discuss it, and most interesting of all is a passage from Serapion the younger (*ca.* 900 A. D.) who describes the following methods of trying whether the theriac be good: First, give of it to the amount of a drachm to a person who has taken a powerful emetic or cathartic, such as scammony or hellebore, and if it counteract the effect of the medicine that has been taken, we know that it is genuine. Second, as Galen directs, having got a wild cock, allow it to be stung by a venomous reptile, and then give it a proper dose of the theriac. If the fowl escape unhurt, we are sure that the medicine is good; but if he die we know that it is not to be depended upon. Third, give a poisonous substance, such as opium, to a cock or dog, and then administer the theriac, the powers of which may be judged of from the result. Here we have a series of biological tests as scientific as some of those used in modern serum laboratories.

The treacle of Andromachus followed the Crescent even to Cairo and India, whence we shall hear of it later. In the Moslem universities of Spain it was of course taught to physicians, and hence took hold in Europe, for when the Moors were expelled by Ferdinand and Isabella they left behind their scholarly traditions and their Arabic manuscripts, so that a little beacon was left burning in that "windy night of time." There are a dozen extant theses and treatises from all the European countries, touching upon the virtue of the drug, especially in the plague; and as I have said, the theriac is recommended in every book on fevers and poisons until nearly 1800. Thus Daniel Defoe, in *A Journal of the Plague Year*, quoting his "particular friend, Dr. Heath":

"Only that," says he, "some recommend one thing as most sovereign, and some another. Some," says he, "think that *pill ruff.*, which is called itself the antipestilential pill, is the best preparation that can be made; others think that Venice treacle is sufficient of itself to resist the contagion; and I," says he, "think as both these think, viz., that the first is good to take beforehand to prevent it, and the last, if touched, to expel it." According to this opinion, I several times took Venice treacle, and a sound sweat upon it, and thought myself as well fortified against the infection as any one could be fortified by the power of physic.

The remedy was indeed so famous that its name became in several languages a general term denoting any antidote. So the Man of Lawe's comparison:

Christ, that which is to every harm triacle.

And Chaucer tells us, too, that a store of the remedy was in demand upon the immortal pilgrimage:

Seyde I nat wel? I cannot speke in terme;
But wel I woot, thou dost my herte to erme,
That I almost have caught a cardiacle.
By Corpus bones! But I have triacle,
Or elles a draught of moyste and corny ale
Or but I here anon a merry tale,
Myn herte is lost for pitee of this mayde.
(*Words of the Host to the Physician.*)

Some sub-editions of the "Bishops'" English Bible of 1568 are called by bibliographers the "Treacle Bible," on account of their rendition of the very familiar verse, Jeremiah viii, 22: "Is there no *tryacle* in Gilead? Is there no physician there?" (The Douai Bible has the same verse less poetically, thus: "Is there no *rosin* in Gilead?")

A few men raised feeble voices against the theriac during all these centuries. Three of them get a hearty scolding from Diemerbroeck:

Capivaccius, Trincavellius, and Julius Alexandrinus alone are silent, and try to exterminate from medical practice this divinest and most useful of drugs.

Trincavellius seems also to have held the heretical opinion that the plague was a hot disease and not to be treated with sweats and calorifics. Besides these three culprits, one Vincentius Calzavelius, a physician of Brix in Bohemia, wrote in

1570 a thesis *De theriacae abusu in febribus pestilentibus* upholding the same view. So far as I know, these were the only medical men who opposed the use of the drug, and the two of them, whose works I have examined, opposed it in the pestilential diseases only, not objecting to its use in other ailments. Robert Burton, the anatomist of melancholy, has a polemic against treacle and all other compound prescriptions, but then he was no physician, but a clergyman, and as he says himself, like a ranging spaniel barked at every bird he saw.

The drug could not only be used directly, but was often made an ingredient of other prescriptions, and was put into powders, electuaries, potions, waters, pills, ointments, and plasters. There were several grades of theriac in commerce, according to the place of manufacture, as that of Paris, of London, of Venice, and so on. Since Venice, with its great fleet, had the most direct trade with the Mediterranean lands whence most of the ingredients came, its product was considered the best. From this fact the medicine was called by the name commonest in English books, Venice treacle. Then there were modifications of the formula, such as those of Monavius the German, of Edinburgh, and others. There is an apt passage in Burton's *Anatomy of Melancholy:*

Mellichius, Cordus, Wecker, Quercetan, Renodeus, the Venetian, Florentine states have their several Receipts and Magistrals: They of Noremberge have theirs, and Augustana Pharmacopœia, peculiar medicines to the meridian of the City: London has, every City, town, almost every private man hath his own mixtures, compositions, receipts, magistrals, precepts, as if he scorned antiquity and all others in respect of himself. But each man must correct and alter to shew his skill, every opinionative fellow must maintain his own paradox, be what it will; *Deliriant reges, plectuntur Achivi:* they dote, and in the meantime the poor patients pay for the new experiments, the Commonalty rue it.

There was a disagreement between the Colleges of London and Edinburgh as to the manner of preparing the viper's-flesh[3] which was used in making the theriac, London apparently preferring the imported article in the form of troches, whereas the wise men of Edinburgh held that a fresher and therefore better product could be made from native vipers.

A learned discussion on "Troches of Vipers for the Theriac" ends thus:

Take of Viper's-flesh after the skin is stripped off, the fat and entrails being taken out, 8 ounces; of the finest wheaten Bread, or rather Bisket, powdered and sifted, 2 ounces. Let them be formed into little Troches, by anointing the hands with Opobalsam, or Oil of Nutmegs by expression; then dry them upon the bottom of a sieve inverted in some open place, where the air hath passage through; and turn them often till they are thoroughly dry. . . . Vipers are frequently brought to us from several parts of *Italy*, and particularly from *Venice*, but they that lay most stress upon them, chuse rather to be the preparers themselves with our own Vipers here; which at the proper time of year are full as good, and the Troches are much the better for being fresh; which they cannot so well be when they come from abroad. The College of Edinburgh prefer the dried Viper's-flesh to the Troches thereof.

The formulæ varied so much by this time that Johann Nolt of Lübeck thought it worth while to print a large table giving in parallel columns 11 formulæ for Andromachus' theriac, for purposes of comparison. The Orviétan celebrated by Molière[4]

O grande puissance
De l'orviétan!

was one of the complicated mixtures based upon theriac.

One of the most notable theriacs was that of Matthiolus, court physician to the Emperor of Austria about 1550. His prescription contained 127 ingredients, one of which was ordinary theriac, itself containing fifty-odd more substances, to say nothing of a half-dozen other compounds thrown in for good luck. Diemerbroeck calls it

famosa illa antidotus, magna illa congeries plurimorum simplicium sine ordine, sine methodo, sine ulla ratione simul congestorum ac conjunctorum.

This masterpiece reigned as the king of drugs until Joseph Duchesne, (Latinized *Quercetanus*) invented and published in 1607 a theriac so surpassing in its powers that he called it *Benedicta*, the blessed. Not even content with such a blessing, Frederic Greif, of Tübingen, took in hand the Blessed Treacle, boiled it down to the consistence of a pill-mass and added various substances until he evolved a prescription of 150 ingredients, and so mighty in its virtues that it was called the Exalted or Celestial Treacle.[5]

It must be remembered that the therapeutists of that time did not desire drugs to meet single indicated symptoms, as in modern medicine, but just as the alchemists were searching for the universal element, so the pharmacists were ever seeking a universal remedy, wishing to place beside the Philosopher's Stone an equally magical Physician's Stone, potent to assuage all disordered humors, to charm away all ailments at a single stroke, and valuable in every diverse condition. Christianus Paullinus (1643-1712) published a treatise on the Celestial Theriac, giving an index of lesions curable therewith, which covers the entire catalogue of diseases, including "all the external and internal malignancies" from nightmare through toothache and "obstruction of the spleen" to scabies.

Of course these medicines, composed of such numerous ingredients, most of them exotic and many rare, were very expensive and to be had only by the rich. Therefore, there was a cheap kind, the *theriaca diatessaron*, made for the poor, having only five ingredients (gentian, laurel-berries, birthwort, juniper-berries and honey) but in spite of its simplicity, "excellent against fevers and poisons." I like to fancy that the sulphur and molasses, "spring medicine" of our great-grandmothers, was a poor relation of the celestial sulphur-and-honey of Tübingen.

The fame of theriac was so great that the drug passed out of the hands of legitimate physicians, and became an article of commerce among the people. To that rascally mediæval army of peripatetic mountebanks, palmers, mendicant friars and pardoners, was added a troop of *triacleurs*, who wandered from place to place selling their nostrum to the rustics. Bern-

[3] See Quincey's Dispensatory, London, 1749.

[4] L'amour medecin, Act II.

[5] *Vide* Rosa, *De theriaca coelesti*, 1703.

hard, in his little volume about theriac in France, quotes the title of an old farce, "Le Pardonneur, le Triacleur, et la Tavernière," and prints a magistrate's license of the sixteenth century, allowing a friar and a triacleur to travel in company; a convenient arrangement which permitted a layman to buy pardon for his sins and balm for his diseases from the same firm. Needless to say there were many tricks of the trade and plenty of fraud in the treacle business.

"I remember," says Matthiolus, "seeing one of these fellows who gave his boy 'poison' substituted in this sleight-of-hand way, and then pretended he would not give medical aid until the boy's pulse ceased and he was at the brink of death, in order to prove the power of his false and adulterated theriac. Having first admonished the sly youth to repress his respiration, to change color, to roll his eyes, and to contort his face, the demonstrator called to his side a physician who was among the bystanders (not a very shrewd man, to my way of thinking) and requested him to testify publicly that the boy's pulse had ceased. The good doctor, so thoughtlessly made the dupe of the peddler, announced to all that he found no pulse in the boy; which he might well say, since the fellow knew how to stop his pulse, as Galen describes, Lib. 6 *de placitis Hippocratis*, where he says 'arteries, like nerves, if cut or compressed, are deprived of all pulse and vibration.' They had contrived to put a cord about the boy's upper arm. . . . After that young scalawag had taken the quack's medicine, he gradually worked the cord loose and finally returned to a natural condition."

The tricks and frauds of such villians as these were taken as a great insult by decent physicians like Matthiolus, and by honest apothecaries. In self-defense, therefore, in the seventeenth century the regular profession began to hedge about the preparation and sale of theriac with divers laws and customs tending toward uniformity. The drug was often compounded in the public presence by reputable men, in order that the populace might know that everything was done in proper manner. The first of these public confections of theriac was held at Montpelier in 1606 by Maître Catalan, chief apothecary of the city. He set a fashion, which was thereafter continued, of publishing a book in Latin, containing a discussion of the history and nature of the drug, together with certificates from the authorities that due care had been taken in the work. The best-known man connected with such performances was Thomas Bartholin, the Danish anatomist, who made theriac in 1671. He had a certificate from the faculty at Padua that the pastilles of Italian vipers they had sent him were freshly and skillfully prepared.

About this time there began to be sumptuary laws or at least regulations of the apothecaries' guilds, forbidding apothecaries to make the drug without permission.

At Paris, the public preparation of theriac took a very elaborate form. We learn from M. Planchon that Moses Charras, "The King's Chief Operator in His Royal Garden of Plants," was the first to make it publicly at Paris (1670). The participation of Charras would undoubtedly lend dignity to the affair, since he was a man of note and author of the *Royal Pharmacopœia* which I have already quoted, a work which was translated into many languages, even into Chinese. A little later the official preparations were held by the Compagnie des Marchands Apothicaires, who yielded their privilege in turn to a Société de la Thériaque open to master-apothecaries, with a large capital and full authority to compound the remedy. Apparently the last public preparation was made in 1790.

These solemn ceremonies lasted from 15 to 17 days, beginning at 5 A. M. The session was opened by the presidents of the college of apothecaries and the faculty of medicine, the lieutenant-general of police and the king's procurator. The person to whom had been given the honor of making the theriac addressed the audience, lauding the virtues of the drug, usually with many quotations from the ancients and much show of oratory. He then gave a scientific description of the ingredients, exhibited them to the public gaze, and finally weighed and mixed them. The finished product was stored in a porcelain jar 88 centimeters high, (still extant in Paris) which was locked with three locks, the keys of which were held by three officials high in the councils of the apothecaries. Several times during the fortnight of preparation there were addresses and collations.

It is easy to see the psychological and financial advantages of such pomp and circumstance. Imagine the effect of a public preparation of Peruna on Mount Vernon Place in Baltimore, with addresses by the mayor and the state chemist, the medical faculties attending in academic robes, assisted by Sousa's band!

It is astonishing that this pedantic fol-de-rol went on without a word of protest for so many years. But a bold opponent was lying in wait—no less a person than William Heberden, he of "Heberden's nodes." In his "*Antitheriaca*—An Essay on Mithridatium and Theriaca," a little volume published in 1745, he makes a caustic attack upon Venice treacle, so level-headed and withal so learned, that I wish time permitted to read the whole 19 pages. Let the following suffice here:

MITHRIDATES, the famous King of Pontus, had a strange affectation of superior skill in the powers of Simples. His Courtiers, we may imagine, flattered him upon it, and he has accordingly been delivered down to us as a second Solomon. Whereas if we consider the little leisure that he had for his own inquiries into this part of nature, or the little helps that he could have from the people about him, we must conclude that his knowledge was very inconsiderable. However, Pompey seems to have been possessed with the vulgar opinion and, after he had conquered this King, took uncommon care to secure his writings, in hopes of some mighty treasures of natural knowledge. He was soon convinced of what he might easily have foreseen, and is represented as laughing at the disappointment of his own credulity, when instead of those great arcana, he found only one or two trifling receipts.

There were probably some artful people at this time, who were not disposed to part so easily with the great expectations that had been raised, nor to lose this fair opportunity of enriching themselves by a plausible imposture; which has since been several times repeated and is frequently practiced among us at this day. For soon after, there was published in Rome a most pompous medicine with the name of *Antidotum Mithridatium*, which was pretended to have been found among his papers: though Plutarch, who gives a minute detail of them (mentioning the Love-letters and several interpretations of Dreams), says not one word of this famous medicine; which one can hardly think that he would

have omitted if he had found the tradition supported by any proper testimonies. The authority of Q. Serenus Samonicus is more positive, who says that, notwithstanding the many receipts of *Mithridatium* that were handed about, the true medicine found in the cabinet of Mithridates was only that trivial one consisting of 20 leaves of rue, two dried figs, one grain of salt, and one nut. So that there is some reason to suspect that Mithridates was as much a stranger to his own antidote as several eminent physicians have since been to the medicines that are daily advertised under their names.

And so on, with many quotations from erudite works of all ages, for Heberden will fight with authority, he says, that which is defended by authority. He points out that one of the great reasons for the popularity of treacle was the mediæval fear of murder by poison, which led people to make much use of antidotes. But the only poisons known when the treacle was composed were hemlock, aconite, and the venoms of beasts. How then could the drug be of use against the newer poisons, such as arsenic, quicksilver, and the like? Moreover; first, the formula has never been the same for a hundred years together; second, there is grave danger of error and overdosing when opium is given in such complicated mixtures; third, to give theriac is to load a sick man's stomach with useless things; fourth, whatever effect the theriac has can be gained with a few simple drugs.

Allow me to quote one more paragraph, that in which he comes to a brave conclusion:

It still goes on to be prepared in the old manner, as near as may be, in all the great cities of Europe. Its power indeed and fame has of late been manifestly declining; and we may hope that its reign will not last much longer. Enough has surely been given to antiquity: let not length of time, which has ever been the fatal enemy of falsehood and imposture, be made in this instance to support and protect them. Perhaps the glory of its first expulsion from a public Dispensatory was reserved to these times and to the English Nation; in which all parts of Philosophy have been so much assisted in asserting their freedom from antient fable and superstition; and whose College of Physicians in particular hath deservedly had the first reputation in their Profession. Among the many eminent services, which the authority of this learned and judicious body hath done to the practice of Physic, it might not be the least that it had driven out this medley of discordant Simples, which, perhaps, has no better claim to the title of *Mithridatium*, than as it so well resembles the numerous, undisciplined forces of a barbarous King, made up of a dissonant crowd collected from different countries, mighty in appearance, but in reality an indifferent multitude, that only hinder one another.

Heberden promptly followed up his words by deeds, and forced a vote in the College of Physicians, on the expulsion of theriac and Mithridatium from the London Pharmacopœia. It is said that when the ballot was taken there were 13 votes in favor of retaining the theriac, 14 against it. Thus came to an ignominious defeat, in an English committee-room, after a glorious career of 2000 years, the greatest medicine of all the world.

Although Heberden had dealt the death-blow, the theriac was to linger on a while in many parts of the earth. Alexander Monro, Senior, cured himself of a bad angina by its use, as late as 1781; and Benjamin Bell says that in his time it was in frequent use in England as an application to ulcers.

In 1835, Dr. Malcolmson of Madras was told by some of his native patients of a drug which had worked wonderful cures in beri-beri called Teriak Farook. He was able to purchase some of it in India, finding it in cannisters bearing Turkish characters stating that it was invented by a famous Turkish doctor called Andromakoo, in the fortified city of Vendeck. He found, however, on pulling off the outer label, another showing that the material really came from Venice; it represented, therefore, the last trace of that once-mighty commerce of Venice with the East. The word *farook*, applied to the drug, is explained by a passage in Prosper Alpinus,[6] who states that in his time theriac was in much use by the Sultan at Cairo, and was called *Tharach faroch*, as Mahomet called his successor Omar faroch, the unsurpassed. In 1837 Maxwell of Calcutta read Malcolmson's article, found some theriac in the bazaars, and tried it on himself and many beri-beri patients without result.[7] This is the last recorded use of theriac, in the realm and reign of Queen Victoria the Good, 1899 years after the death of Mithridates.

[6] *De medicina Aegyptorum*, 1591.

[7] Indian Jour. Med. and Phys. Soc., 1837.

IS PATHOLOGIC METABOLISM IN THE PARENTAL ORGANISM RESPONSIBLE FOR DEFECTIVE AND MONSTROUS DEVELOPMENT OF THE OFFSPRING?*

By E. I. Werber, Ph. D.

(From the Marine Biological Laboratory, Woods Hole, Mass., and the Department of Biology, Princeton University.)

One of the most interesting and most difficult problems of pathology as well as of general biology is that of the causes underlying defective, atypical development. Leaving out of consideration the "explanation" which was given by superstition, and which was generally accepted until in recent times it had to retreat before scientific investigation, we find, besides crude theories of mechanical interference with the developing embryo, mainly two theories which seem to offer a reasonable explanation.

A very significant suggestion has recently been made by F. P. Mall[1] in his monograph on the causes underlying the origin of human monsters. He states that a careful study

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of a collection of 163 pathological embryos has led him to assume that the defective development of these embryos was due to a condition which he terms "faulty implantation" of the ovum in the wall of the uterus. According to his view, which seems to be well supported by clinical data, this defective implantation is due to a diseased condition of the uterus. The imperfect implantation of the ovum in the uterus would, he concludes, make its adequate nutrition impossible, thus bringing about defective development and eventually leading to the embryo's early death from inanition. According to this theory, therefore, which seems to go far towards accounting for monstrosities in embryos aborted during the first two months of pregnancy, a healthy ovum may give rise to a monster when discharged into a diseased uterus where it fails to become properly implanted.

Another important hypothesis was advanced by O. Hertwig [1] in 1896. Concluding from his experiments in which he could produce spina bifida in amphibian embryos by subjecting the fertilized eggs to the action of 0.6 per cent to 0.7 per cent solutions of sodium chloride, Hertwig suggests that the formation of monsters in human beings may possibly be due to the presence of certain poisons, such as alcohol, or toxines in the blood of the mother. This seems to be a very valuable hypothesis, and had it attracted the attention which it justly deserves, we might by this time be able to answer many a question in teratology and possibly also in general medicine, which thus far has eluded attempts at inquiry.

Hertwig's suggestion seems to find ample support from discoveries which have been made in recent years. For experimental teratology has shown us that there are various physical as well as chemical means by which the development of the ovum can be caused to deviate from the norm or even to become monstrous. And the recent researches of Féré,[2] Stockard [3] and McClendon,[4] who obtained one-eyed monsters by submitting developing eggs to the action of such injurious substances as magnesium chloride, alcohol, ether, alkaloids, etc., would seem to indicate that the monsters found in nature may also be due to the effects of chemical agents.

With this in mind, in the summer of 1911, I performed a number of experiments on the eggs of the marine teleost fish *Fundulus heteroclitus*. Thinking that the monsters found in nature might possibly be due to an excessive retention of nitrogenous waste compounds in the blood of the mother during pregnancy, I submitted the fertilized eggs in very early cleavage stages to the action of solutions of sodium nitrate and potassium nitrite in sea-water. Although in these experiments I did obtain cyclopean monsters in both nitrate and nitrite solutions, the percentage of the eggs developing in this manner was so low that the results could not be considered as conclusive. Possibly more experimentation is needed in order to obtain more definite results with these chemicals, but I have never repeated them again, thinking that the substances which are found in the urine of individuals afflicted with certain diseases of metabolism may be more toxic and thus more likely to cause pathologic development of the embryo in the uterus of a mother whose metabolism has been seriously impaired.

As a preliminary test of this hypothesis, I carried on during the past summer some experiments on the fertilized eggs of *Fundulus heteroclitus*. The eggs were submitted in early cleavage stages (2 to 4 or 4 to 8 and 8 to 16 cells, respectively) to the action of solutions of a number of toxic substances known to be found in the urine of persons suffering from disturbances of metabolism. Only two substances, butyric acid and acetone, have so far given me definite results.

When fertilized fundulus eggs were exposed to the action of a 1/12 to 1/14 gram-molecular solution of butyric acid in sea-water for about 15 to 20 hours and then transferred to sea-water, a very large number of them gave rise to monsters. This was also found to be the case in solutions of acetone. Here the eggs were exposed in a number of dishes to the action of solutions of 20, 25, 30, 35, 40, 45 and 50 cc. of a gram-molecular solution of acetone added to 50 cc. of sea-water. A varying number of monsters were found in all dishes, the relative number of them increasing with the strength of the solution up to 40 cc. of acetone, and decreasing in solutions still stronger, which caused the death-rate of the eggs to increase. The results obtained in both series of experiments, with butyric acid and acetone, being very much alike, it will not be necessary to enumerate separately the deformities produced by each.

Cyclopia, asymmetric monophthalmia and mikrophthalmia were found to occur very abundantly. Several cases of asymmetric monophthalmia were found which differed from others of this category, in that an apparently free eye had developed on the yolk-sac at a considerable distance from the embryo. Probably the most striking of the results obtained in this investigation were seen in certain eggs in which could be observed a solitary eye, while nothing else could be seen to indicate the presence of even a deformed embryo. It is difficult to know just what may have happened to that part of the germ-disc which was to form the rest of the embryo. Such cases as this, and others which were obtained by experimentation, confront us with one of the most difficult problems of biology, because they obviously elude all attempts of interpretation, the sequence of events being obscured. Practically all other known deformities of the eye, such as coloboma, total blindness, or presence of lenses only, or presence of supernumerary lenses, were frequently found. Great numbers of eggs developed into anterior half-embryos similar to those which were first obtained experimentally by Roux [5] in the frog. These hemiembryos nearly all exhibit high degrees of malformation, but in some of them a functioning though rudimentary heart could be observed.

Many embryos exhibited defects of the ear-vesicles, which had swollen up to an unusually large size. Others were apparently hydrocephalic, their heads being enormously enlarged. In some embryos large œdematous swellings were also found in other parts of the body.

Various deformities of the heart and blood-vessels were

found in all malformed embryos, except in some cases of median cyclopia. Some possessed no heart at all, while in others it was more or less rudimentary, though usually functioning if present at all. The rate of the heart beat varies with the degree of the abnormality of the organ, and is, as a rule, very sluggish in all monstrous embryos, excepting those in which the only defect superficially noticeable was cyclopia. The range of variation in the development of blood-vessels is also very wide. There may be merely blood-islands scattered on the yolk-sac, rudimentary, imperfectly connected, or in some instances more or less normal vessels.

The tendency of butyric acid and acetone to produce twins seems to be very slight, for I have recorded the occurrence of only a few such cases in my experiments.

It would be far beyond the limits of the present communication to describe, no matter how briefly, all deformities which I observed in these experiments. This will be done in another publication, as soon as a careful microscopic examination of the collected material may permit it. For the present it will suffice to state that an unusually great variety of monsters were found to occur when fundulus eggs were subjected to the action of solutions of butyric acid and acetone. Most of the monsters observed resembled morphologically very much those which have so often been described in human beings.

Other toxic substances, found in pathologic conditions of metabolism, have also been tried, but the results obtained so far have not been conclusive and call for further investigation.

Let us now see what conclusions may be drawn from these experiments. It was shown that butyric acid and acetone have a very injurious effect on the fertilized ovum, causing it to develop in a highly atypical, monstrous manner. The monsters thus produced resemble morphologically those known to occur in nature in the human being and in other mammals. Does this not suggest that the monsters—or at least a great number of them—found in nature may be due to the action of any one of these or other substances in the human body associated with pathological conditions of metabolism? The disturbances of metabolism may vary in degree and the quantity of the toxic substances, which they produce in the body, would vary accordingly. Such variations in the quantity of toxic substances in gravid females may account for the variations in degree of injury exhibited by defective embryos aborted at different periods of gestation or even for some defects found after full-term birth in individuals which may even be apparently normal. I am inclined to think that careful clinical family records may amply justify this assumption.

This hypothesis, that the pathological condition of the embryo or full-term offspring, respectively, may be due to parental pathology, if borne out by positive results of experiments on mammals, may eventually furnish us a secure, scientific basis for the etiology of many congenital defects of the sense organs, the central nervous system (responsible for such conditions as hydrocephalus, epilepsy etc.) and other organs. Some of these defects may pass unnoticed, until the individual is well advanced in life. Furthermore, the effects of an intra-uterine or possibly even pre-uterine poisoning of the embryo or germ-cell, respectively, may not always manifest themselves morphologically. The influence of very small traces of toxic substances due to the pathologic metabolism of the mother (or possibly even the father?) may be slight enough to cause in the organism only certain chemical, unaccompanied by gross morphological, changes. These chemical changes may lead to what I would term a gradual deterioration of the chemical make-up of the individual, the effects of which may become fatal at some point of his life. It is not even inconceivable that such a deterioration may be inheritable and thus eventually lead to racial degeneration. To this latter assumption I am led by the remarkable results which Stockard[1] obtained by breeding in various combinations animals, whose ancestors had been exposed to very long periods of almost constant intoxication (six days of the week) from the inhalation of alcohol fumes. He finds that the results of matings of apparently normal animals of alcoholic parentage deteriorate in a very marked degree with each consecutive generation. There is a relative increase in the still-born litters, increase of the death-rate of the living young and also an increase of animals with congenital defects of the eyes in the third generation as against the second generation.

I do not doubt but that similar and possibly even more marked effects may eventually be found for the toxic substances of pathologic metabolism as compared with those observed by Stockard in his alcohol experiments. The validity of this assumption may be easily tested by mating mammals in which disturbances of metabolism had previously been experimentally produced, and by breeding their offspring. Should the results bear out the contentions of my hypothesis, we shall then know what agents nature employs in causing development (individual or racial) to deviate from the norm. If monstrous or defective development could thus be controlled experimentally, means might eventually be found by which their occurrence could be checked. In view of what has already been said above, it seems needless to dwell any longer on the medical significance of the problem.

It will be the task of the experimental biologist to determine what mechanism may be involved in the action of the toxic products of metabolism on the developing organism. This, however, may be done best, after a large enough body of facts has been established to warrant some morphological generalizations.

Since only experiments on mammals would, in my opinion, furnish the crucial test of the assumption that defective development is due to intra-uterine or pre-uterine poisoning by metabolic products of the embryo or germ-cell, respectively, I intend very soon to enter upon this work. I am inclined to predict that the results will eventually bear out the hypothesis.

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MEDICINE IN CHINA.

REVIEW OF REPORT OF THE CHINA MEDICAL COMMISSION OF THE ROCKEFELLER FOUNDATION, NEW YORK, 1914.

In this report of 113 pages are presented the results of the investigations during 1914 of the commission appointed by the Rockefeller Foundation "to study and report on conditions of public health and medicine in China." The commission, composed of President Judson of the University of Chicago (chairman), Mr. Roger S. Greene, American Consul at Hankow, Dr. Francis W. Peabody of Boston and George B. McKibbin (secretary), spent several months in China and visited 17 medical schools and 97 hospitals in China and Manila. Various universities and secondary schools were also visited and numerous conferences held with medical missionaries, government officials and other persons of influence.

In a discussion of the general health conditions, the report states that in China the death-rate is probably higher than in any other known country. The most destructive and widespread diseases are tuberculosis, hook-worm disease and syphilis. Leprosy also prevails. Small-pox is looked upon by the people as a matter of course. The various activities of a public health service as practised in Western lands are almost unknown and isolation hospitals for contagious diseases hardly exist. On the other hand, as the result of the ravages of the plague in Manchuria in 1910-11, a plague prevention service, with several plague hospitals, has been established, and in Canton, Changsha and Nanking a beginning has been made in organizing public health work. No progress has been made, however, with reference to a central public health department.

The native Chinese practitioner is not subject to legal requirements. Anyone who wishes may announce himself as a physician and practise as he pleases. Diagnosis in the main is based on the pulse; and Chinese treatises indicate no less than 98 different types of pulse. A common method of treatment is that of puncturing the body with a needle. The *materia medica* is mainly one of herbs, but some modern drugs, as quinine, are commonly used. Modern patent medicines have a large sale. The Chinese practitioners, although claiming a knowledge of medicine, admit that they know practically nothing about surgery. This is doubtless due to their ignorance of anatomy. The dissection of the human body is contrary to the ideas of the Chinese relating to the future life and is regarded with peculiar horror. (It was not until November 22, 1913, that autopsies and dissection were officially authorized throughout the republic.)

Some physicians trained in Western medicine are found practising in China, but these, with few exceptions, belong to the mission hospitals and the various treaty ports.

The medical schools are discussed under (1) government and private schools, (2) missionary schools, (3) schools for Chinese women, and (4) non-missionary medical schools under foreign control. The strictly Chinese schools have been laboring under great disadvantages during the past four years, on account of disturbed political conditions and the strained finances of the government. Government control is still incomplete and the classes, considering the limited funds, are too large. All the Chinese schools are "greatly handicapped by the fact that not one of them has access to a really satisfactory hospital. It is evident that there is no medical school now in China which is adequately equipped and no school which is adequately manned. Some of the schools under foreign control, however, have really high ideals, and the advanced men on other faculties have the right policies in mind."

China has three medical schools for women alone, besides two in which they may be taught with men. These schools, however, are small, poorly equipped and ill-prepared to train competent physicians. Moreover, they are hampered by the inability to get a sufficient number of girls with a proper preliminary education. The commission concludes that for the present such women as are peculiarly fitted for the profession might better be sent abroad for a thorough training.

The non-missionary schools under foreign control are five in number: Japanese in Moukden, German in Tsingtau and Shanghai, French in Canton and English in Hongkong.

The commission found that a study of hospitals in China "resolves itself almost completely into a consideration of the mission hospital. The more important non-missionary hospitals established by foreigners are for the care of foreigners and have no very definite influence on China itself. The hospitals under Chinese control, whether government or private, are with few exceptions, ineffective and they are chiefly of interest as demonstrating how small an impression high-grade Western medicine has as yet made on China."

A point which the report repeatedly emphasizes is the need of more graduate nurses with foreign training. At present there are only 140 foreign nurses in the country and these are distributed in about 100 hospitals. A great need is enough foreign nurses to serve as teachers in the leading training

schools, which, if thus equipped, would be then capable of furnishing Chinese nurses.

The recommendations of the commission may be briefly summarized as follows:

That the Foundation should undertake medical work in China and as far as possible should cooperate with existing missionary institutions.

That medical instruction in which the Foundation is concerned should be on the highest practicable standard, that is, a standard corresponding to the American high school, supplemented by two years of pre-medical work in English, Chinese, physics, chemistry and biology. English should be the language of instruction, supplemented if necessary by explanations in Chinese.

That the time is not yet ripe for the Foundation to assist in the organization of a large work in relation to public health. A useful foundation for such work might, however, be laid by assisting one or more local hospitals.

That it is not advisable at this time to establish an independent institution for research, but that research be encouraged in connection with the medical schools aided by the Foundation.

That the first medical educational work be in Peking in connection with the Union Medical College; that a new school be established in Shanghai and provisions be made for cooperating with existing schools in and near Shanghai in order to unify medical effort in the lower Yangtze Valley; and that assistance be given the Canton Christian College and that the Yale Mission at Changsha be aided in its medical plans.

That two model tuberculosis hospitals be established.

That six fellowships, yielding $1,000 and necessary traveling expenses, be maintained to enable selected Chinese graduates to study abroad.

That scholarships be established in the schools aided by the Foundation in order to encourage selected young men, with insufficient means, to study medicine. Ten such scholarships are suggested for 1915-16 and ten additional yearly until the total number reaches fifty.

That the development of hospitals be aided by:

(a) Paying the salaries of additional foreign medical men to be assigned to hospitals already established.

(b) Paying the salaries of Chinese doctors who will work in the hospitals under foreign doctors for considerable periods of time and thus secure adequate practical training.

(c) Supporting a considerable number of foreign nurses.

(d) Increasing the equipment of certain hospitals and more particularly those in connection with medical schools.

(e) Providing in some hospitals the salary for a business manager.

(f) Establishing central diagnostic laboratories in Peking and Shanghai.

(g) Establishing at least one, probably two, extensive libraries of current medical literature.

That the training of nurses be aided by:

(a) Providing dormitories in special cases in connection with schools for nurses.

(b) Establishing scholarships (not over five at first) to enable Chinese women to receive training in the United States.

(c) Translation into Chinese of text-books on nursing.

That from time to time, as may appear expedient, specialists in various branches of medical sciences be sent to China to lecture in medical schools aided by the Foundation.

That provision be made for ten fellowships annually for medical missionaries to enable them to proceed to the United States or Europe for advanced study, and that the annual stipend be $1,500, with $1,000 for expenses.

Other recommendations concern a resident commissioner and an advisory committee.

It is at once evident that these recommendations embody a broad plan of medical education which has for its ultimate object a national system of public health administration. Emphasis is laid upon the opinion that to ensure its final success it is essential that a large number of native physicians be thoroughly trained in the methods of Western medicine. Not all the recommendations can be acted upon at once, and that they cannot, the commission apparently fully realizes. However, their adoption as rapidly as may be possible, if approved by the local and national governments, will not only diminish pestilence and its consequences, but will as a result do more than any other single factor in aiding the economic and social progress of the new republic.

RICHARD M. PEARCE, M. D.,
University of Pennsylvania.

A CASE OF ABSCESS OF THE LIVER, DUE TO A STREPTOTHRIX.*

By ARTHUR BLOOMFIELD, M. D.,
AND
STANHOPE BAYNE-JONES, M. D.

The patient, P. K., aged 32, was admitted to the medical service (Gen. No. 98,529), on October 5, 1914, complaining of "stomach trouble." He came to this country from Russia fifteen years ago, and since then has been occupied as a cigarmaker. Four years ago, however, he went on the road, through the southwestern states, for a year and a half, and then for another year was in the junk business. During the past year he has again been in the cigar factory.

His general health has been good. He is aware of no sores or skin lesions of any sort. There is nothing to suggest a previous

* From the Medical Clinic of The Johns Hopkins Hospital.

dysentery. Appetite and digestion good. Constipation for the past few years. His teeth have always been bad.

The patient dates his trouble from an upset of the stomach after a dose of salts—about a month before admission (Sept., 1914). Following this there was malaise and fever, his temperature rising to 103° F., with sweats at night. He was said to have typhoid. He had no sharp pain, but his most distressing symptoms were "cramps" in the stomach (epigastrium) and anorexia. He vomited once. There was no cough.

On admission, he said there had not been much change in his condition since onset. He looked pale and sick. The teeth were much decayed; there was pyorrhea. The tonsils were not abnormal. There was no particular glandular enlargement. The lungs showed no marked abnormality in the physical signs except over the right back, where dulness was noted above the angle of the scapula, increasing to flatness at the base. Over this area the respiratory murmur was diminished and the voice was lost. Inspiratory descent of the lung, however, was normal and Litten's sign was present on both sides. The abdomen was at first negative, except for tenderness and resistance over the upper right rectus. The liver and spleen were not felt.

The leucocytes were 11,000 on admission, rising on the following day to 17,000, and remaining at about 20,000. There was a polymorphonuclear leucocytosis, no abnormal cells being found. Hb., 93 per cent; R. B. C., 4,600,000. The urine was negative. The Wassermann and Calmette 1 per cent and 5 per cent tests were negative. The temperature was irregular, at times intermittent, varying from 98° F. in the morning to 102° F. in the evening. A blood culture, made on October 10, yielded no growth. Nothing definite was found in the sputum, which was inconstant and small in amount. The X-ray of the chest showed only diffuse infiltration, with no evidence of effusion in the right pleura.

His condition continued the same, the pulmonary signs at the right base remaining indicative of a subdiaphragmatic abscess, rather than an intrapulmonary lesion. On October 11, the liver dulness was noted 7.5 cm. below the costal margin in the mammillary line, and 8 cm. below the ensiform. The liver edge was not felt.

On October 19, an exploratory puncture was made. A long needle was inserted in the 10th interspace in the posterior scapular line. At a depth of 8 cm. pus was encountered, and 5 cc. were withdrawn. It was thick, greyish green, and had a foul, pungent odor. No granules were noticed. Smears showed degenerated leucocytes and cells, and "fibrin and clot-like lumps." No tubercle bacilli and no amœbæ were seen.

On October 20, he was transferred to the surgical service and explored (Dr. McClure). A large abscess was found high in the right lobe of the liver, from which at least a liter of thick, greenish pus was evacuated. This pus had a foul, stinking odor. No amœbæ were found. The stomach and intestines were not observed. The temperature fell rapidly, and after November 7—17 days after operation—remained practically normal. There was free drainage by tube for about a week, and a small sinus persisted, which discharged pus freely.

On November 17, the patient insisted upon going home. He was up and about, feeling well, and declined further treatment. He had gained 16 pounds since operation.

The pus, which was aspirated before operation, was sent to the laboratory for culture. It was planted on the surface of various media anaërobically and aërobically, but most of it was inoculated into deep tubes of ascites-dextrose-agar, by the shake method of Rosenow. The surface plants yielded no growth after several weeks, but, at the end of four days, innumerable small, grey colonies were visible in the deep tubes. These were sharply localized in a zone about 1 cm. wide, and 2 cm. below the surface of the medium. These colonies showed in fresh and stained preparations a pure culture of a delicately branched, mycelial, spore-bearing growth, which seemed to belong to the streptothrix group.

The drainage from the operative wound was then immediately examined, and showed abundant dotted mycelial threads, apparently identical with those seen in the cultures. No granules were found in this material, and no radiating mycelia with peripheral clubs. There were numerous bacteria of many sorts, degenerated cells, and detritus.

Although the solitary liver abscess was the prominent feature of the case, a cryptogenetic infection seemed unlikely and a search was made for a portal of entry. No lesions were found on the skin, mucous surfaces, or in the special sense organs. The stools were normal, and there was no history obtainable to suggest gastrointestinal disease. On close questioning, the patient admitted that off and on, for about two years, he had had a slight cough, with occasional small lumps of sputum. The symptoms were so insignificant that there was more or less uncertainty in his description of them. When under our care he had no spontaneous cough, but after a good deal of effort was able to bring up a small amount of sputum. This specimen consisted of mucus, with opaque pinhead-sized lumps, which, on microscopic examination, were found to consist of degenerated pus cells. Throughout were scattered abundant threads exactly similar to those seen in the abscess discharge. No tubercle bacilli were found. Examination of the lungs at this time showed still considerable impairment of percussion at the right base behind, with faint breath sounds, and persistent fine crackles on inspiration. It was thought, however, that these sounds might depend entirely, or in part, upon the subdiaphragmatic condition.

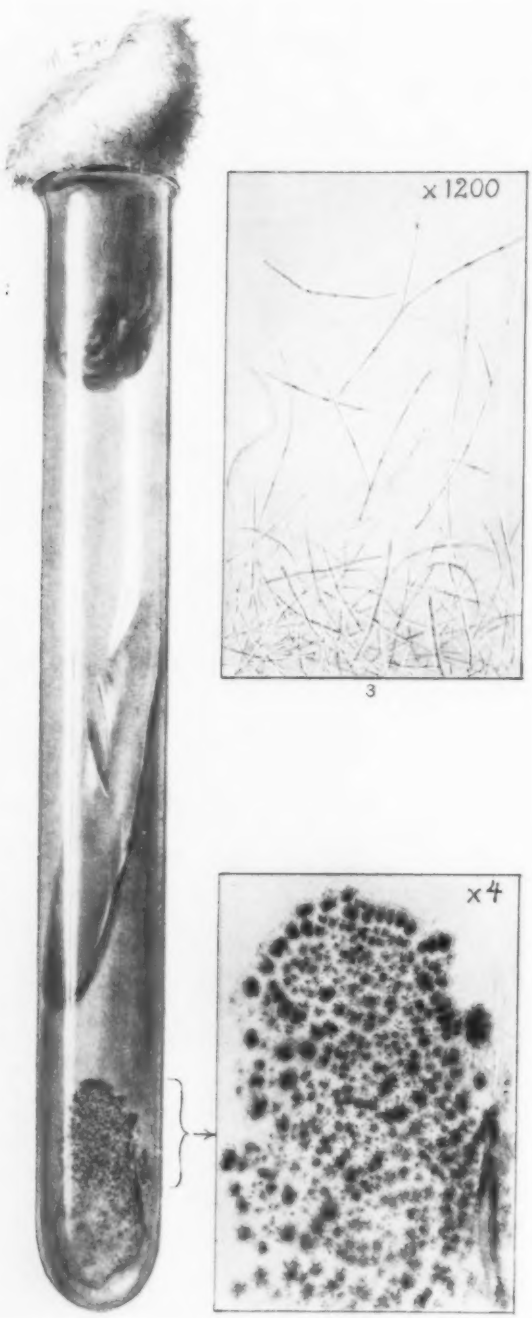
An antigen was prepared by centrifuging a broth culture of the organism (see below), suspending the sediment in 10 volumes of salt solution, and extracting for 24 hours at 37° C. The clear supernatant fluid was used. With this antigen, the patient's serum fixed complement in amounts of 0.1 cc. Normal sera showed no fixation with four times this quantity, and the usual antigenic and anticomplementary controls were clear.

The case is to be looked upon, then, as one of chronic low-grade pulmonary streptothricosis, with a large, solitary liver abscess, from which has been isolated in pure culture the organism found in the sputum. The points of interest are the fulminating character of the hepatic involvement during the course of a practically latent pulmonary disease.

The cases of systemic streptothricosis up to 1912 are summarized in Petruschky's article in volume V of Kolle and Wassermann's Handbuch der Pathogenen Microorganismen, to which reference is made here. Whereas the portal of entry has quite frequently been through the respiratory tract, the metastases are usually generalized. We have found no reference to a solitary abscess of the liver, associated with true streptothrix infection.

Morphological and Cultural Characteristics of the Organism.

The original tubes of ascites-dextrose-agar showed innumerable colonies located in a sharply demarcated zone about 2 cm. below the surface of the medium. The largest colonies reached a size of 1 mm. in diameter; they were grey, opaque, with a slightly darker center and slightly irregular edges. In the hanging drop, the growth was seen to consist of interlacing mycelial threads, not very highly refractile, non-septate, and single-contoured. The threads were about 0.5 μ in diameter and dotted with highly refractile round bodies (spores) especially towards the periphery. True branching was easily and distinctly made out. There was no motility. There was no distinct radiating arrangement of the threads and no peripheral clubs.



1. Seven-day growth in ascites-dextrose-agar, showing deep situation of the organism.
2. Magnified four times, showing general grouping of the colonies.
3. Fresh specimen, × 1200, showing branching and spores.

The organisms stained readily and well with carbol-gentian violet, methylene blue, Bismarck brown, and carbol-fuchsin. They decolorized completely and constantly when stained by Gram, and they were non-acid-fast.

These morphological and tinctorial characteristics have remained quite constant. The organism was subcultured aërobically and anaërobically on ascites-dextrose-agar, on dextrose-agar, plain agar, glycerine agar, blood agar, Loeffler's serum, potato, gelatin, and in plain and dextrose broth and milk. Up to this time, it has refused to grow on any of these media under completely aërobic or anaërobic conditions. A partial oxygen pressure seems necessary, and this has been furnished best by deep tubes of ascites-dextrose-agar, in which the colonies appear after 18 hours at a constant level below the surface. They increase in size until a maximal growth is reached at the end of from six to seven days. At this time, the colonies are about 1 mm. in diameter. They remain discrete. The most abundant growth has been obtained in ascites-dextrose-broth, partial pressure being secured by varying amounts of pyrogallic acid and alkali. Under these conditions, the colonies grow along the walls of the tube, subsequently dropping to the bottom. Individual colonies are easily fished from this medium. The cultures have all had a peculiar foul odor, similar to that of the original pus. Growth does not progress visibly at room temperature, body temperature being the optimum.

ANIMAL INOCULATIONS.

Guinea-pig I. Male. Wt., 320 gm. October 26. Emulsion of one of the original agar tubes intraperitoneally. Nov. 1. Looks sick. Wt., 295 gm. Examination negative. Nov. 20. Looks well, active. Wt., 310 gm. Sacrificed. No lesions found.

Guinea-pig II. Male. Wt., 300 gm. Oct. 27. Emulsified growth from an ascites-dextrose-agar tube subcutaneously into left groin, and deep into hepatic region. Nov. 2. Looks sick, dull. Wt., 275 gms. A firm mass in left groin about 2 cm. in diameter—seems painful. Mass increasing rapidly in size. Explored under ether anæsthesia and found to be a necrotic gland, about 1 cc. of pus obtained. Smears show numerous threads identical with the original culture, and cultures yield the organism pure. Nov. 4. Wound in groin gapes—no tendency to heal, greenish necrotic lining, sero-sanguino-purulent discharge. Skin widely undermined. Animal looks sick. November 7. No change, streptothrix constant in the discharge. Nov. 20. Wound somewhat smaller, tendency to healing. Sacrificed. No internal lesions found.

Guinea-pig III. Nov. 8. One loop of pus from G. P. II injected subcutaneously into left groin. Nov. 15. Fluctuating lump, 2 cm. in diameter, at site of injection. Aspirated; greenish brown pus, shows numerous bacteria and streptothrix threads. Nov. 21. Sacrificed. No other lesions found.

Guinea-pig IV. Male. 330 gms. Ascites-dextrose-agar culture into rt. jugular vein and subcutaneous tissue. Nov. 4. Wt., 305 gms., looks sick. Neck healed but marked induration; a chain of firm glands, from .5 to 1.5 cm. in diameter, extending along right neck into mediastinum. Nov. 15. Gain in wt., glands smaller. Nov. 20. Sacrificed. No lesions found except chain of glands in right neck. Smears from glands negative for streptothrix.

The organism, then, seems to be of low pathogenicity for guinea-pigs, producing no general infection, but chronic localized lesions which tend to heal.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

MARCH 1, 1915.

1. **Exhibition of a Case of Solitary Tubercle of the Brain.** DR. HOWLAND.

R. J. (Col.), 3 years of age. This patient is the youngest of four children, one of whom died at 10 months of age, of pneumonia. The father and mother are young and strong. There have been no miscarriages or still births. There is no reason for suspecting lues and there is no history of exposure to tuberculosis.

He was a full term child, born without instruments after a very easy labor. He was fed at the breast for 14 months. There is no history of any illness during the first year. He had measles at 18 months and pertussis at 2½ years—neither very severe. He has suffered from no other acute infectious disease. There has been no trouble with his ears. He cut his first tooth at the fourth month; he walked well at the eleventh month and could talk at the seventeenth.

He seemed perfectly normal until August, 1914; at that time his mother noticed that he cried less than usual and he has not cried properly since. Just before Christmas it was noticed that his hands trembled when he was feeding himself; there was also some tremor of the body. It was noticed at this same time that, following a cold, his eyes began to droop and in about a week the ptosis was nearly as complete as it is now. Both sides were affected simultaneously. He has never had a nasal voice, regurgitation of food or paralysis of extremities, suggestive of diphtheria. He has grown very nervous and jumps at every noise. He has never had any convulsions. His mother has noticed no change in the child's mentality or in his disposition.

He was seen in the dispensary on February 4, when he could run about normally. He returned and was admitted on February 18. It was noticed that his ptosis was more marked and that it was difficult for him to walk. He has double ptosis, more marked on the right side, with ophthalmoplegia. He can move his eyes only to the slightest possible extent in any direction. His left eye has a tendency to turn in. His pupils are moderately dilated; they react very slightly, if at all, to light.

His tongue protrudes in the median line. When he attempts to cry it is seen that there is a slight loss of power on the left side of his face. He apparently hears equally well on each side. There is a marked tremor of his upper and lower extremities; he stands and walks now with considerable difficulty and this has distinctly increased.

He has no Babinski reflex or ankle clonus; his other reflexes are present and slightly exaggerated.

The course of his disease has been progressively and quite rapidly worse in the three weeks that he has been under observation.

It is obvious that he has something affecting the third, fourth and left sixth nerves and slight involvement of the left seventh. In addition, he shows Macewen's sign, *i. e.*, a change in the percussion note over the parietal regions, a curious cracked-pot sound being elicited. The X-ray shows separation of the sutures and the digital markings characteristic of internal hydrocephalus.

The involvement of these nerves and the hydrocephalus would point to a lesion in the neighborhood of their nuclei, and a lesion which compresses or obliterates the aqueduct of Sylvius. A tumor is the most obvious explanation, it being hard to understand that a degeneration could produce the hydrocephalus. Dr. Dandy has made the interesting suggestion that it might be a tumor of the pineal gland pressing upon the corpora quadrigemina and the aqueduct.

In the last few days some new symptoms have appeared which seem to us to make the diagnosis more clear, that is, there has been a change in the cerebro-spinal fluid obtained by lumbar puncture. This, at the first puncture, contained 30 cells per cubic millimeter; at the second and third, 70 cells, almost all mononuclear, and in the fluid, on standing, a slight film develops.

It would appear that at the present time there is a certain degree of meningitis, which is progressing. The boy has a faintly positive von Pirquet. It seems to us, therefore, very probable that there is a solitary tubercle in the neighborhood of the nuclei of the third and fourth nerves; that this by pressure affects the third and fourth, sixth and seventh nerves; that it also produces hydrocephalus and that, secondarily, he is developing a tuberculous meningitis.

DISCUSSION.

DR. THOMAS: I have been most interested in this case, and Dr. Howland has been good enough to let me see it on a number of occasions. When the patient first came to the dispensary he presented a very different appearance. He then showed nothing but double ptosis with ophthalmoplegia, particularly of the upward movements of the eyes. Just before he came into the hospital he showed some difficulty in walking, and has more lately developed the symptoms of which Dr. Howland spoke. Dr. Dandy's suggestion of a tumor pressing on the corpora quadrigemina was most interesting. Indeed, the case has been most interesting from the start. I had never before seen double ptosis developing in a child, although the congenital form is not uncommon.

In Wilbrand and Saenger's "Neurologie des Auges," which is a veritable mine of medical literature, I find that they record a number of cases of acquired ophthalmoplegia in children in association with a certain number of acute diseases. Wichman has described one case in association with poliomyelitis. I was inclined to regard the condition in this patient as belonging to this unusual group until the other symptoms developed—the peculiar unsteadiness, the tendency to fall backwards, and the curious muscular tremor.

Tumors in the region of the corpora quadrigemina have engaged the attention of physicians ever since Nothnagel first called attention some 30 years ago to the fact that ophthalmoplegia, with difficulty in station and locomotion, often occurred in tumors in this region. The clinical symptoms of a tumor of the corpora quadrigemina, particularly involving the anterior pair, are ophthalmoplegia and the developing incoordination and inability to stand.

Ophthalmoplegia is easily understood by the involvement of the nuclei of the third and fourth nerves. The difficulty in standing is explained by an involvement of the paths from the cerebellum to the red nucleus. Many cases also show deafness, which is due to involvement of the posterior pair of the corpora quadrigemina, and this is often the most pronounced symptom in many of these cases. This child appears to hear well.

The condition of the pupils in such cases is always of great interest. The optic tract, after passing the chiasm, ends in three nuclei—the external geniculate body, the optic thalamus, and the anterior pair of the corpora quadrigemina. The part that appears to end in the corpora quadrigemina is thought by many to carry the fibers which have to do with the light reflexes, and it was hoped that lesions in this region would demonstrate this fact. This hope has not been fulfilled, as the pupils have been found very variously affected in these cases. In the present case the pupils are, I think, practically inactive to light.

The symptoms in this case which suggest involvement of the sixth and seventh nerves are not very pronounced, but if they are to be regarded it makes us think of the possibility of the lesion being a diffuse one at the base of the brain, for the nuclei of these nerves are relatively distant from the corpora quadrigemina. As Dr. Howland has told you, there are evidences of tuberculosis, and a solitary tubercle, in the region suggested by Dr. Dandy with secondary meningitis, seems the best explanation of the case.

2. **Nutrition and Growth.** (Abstract.) Dr. Lafayette B. Mendel, New Haven, Conn.

It seems probable that the food requirement of the growing individual is in a measure specific. Special substances as well as certain proportions of lime, iron or protein are necessary. A comparison of the several food proteins and the tissue protein supposedly replaced or augmented by them excludes the possibility of any direct relationship between the two. In fact, proteins are no longer considered as entities in nutrition, but the significance of the protein *Bausteine* or nutrient units is emphasized. Much study is still needed to state which of the amino-acids or nutrient units of the proteins are indispensable. Glycocoll can be synthesized in the body and consequently a lack of it in the dietary would not be indicated by any nutritive disturbance. Tryptophan does not seem to be produced *de novo* by mammals and disastrous results follow the administration of a dietary free from it. Osborne and Mendel studied, in a diet in which the protein was the sole variable, the nutritive efficiency of various proteins, especially those of composition widely different from the normal tissue protein of the animals used. Rats were fed on a dietary to which isolated proteins in different concentrations were added. Normal growth was secured with some of the proteins, but not with others. The explanation of the failure is suggested by the known absence of certain amino-acids. The decline in growth caused by the lack of tryptophan or lysin can be checked promptly by the administration of these components. Restricted amounts of the necessary nutrient units will also reduce growth.

The absence of carbohydrate from the diet menaces nutritive functions in growth, but at present it is impossible to discriminate for or against any one of the usual dietary sugars.

The indispensability of the true fats seemed to be demonstrated. However, in the method used, lipoids, phosphatides, and vitamines were also removed from the food.

The growth of rats fed on protein-free milk, carbohydrate, and lard was suspended, but could be restored by the addition of unsalted butter, cod liver oil, or to a lesser degree by beef fat.

DISCUSSION.

Dr. Janeway: I can only say a few words of appreciation of what Dr. Mendel has said. Strange as it may seem to many of you, Dr. Mendel and I learned our physiological chemistry at adjoining desks in Professor Chittenden's laboratory some twenty-odd years ago. In those days physiological was an adjective applied to chemistry. It was the ambition of Professor Chittenden that chemical physiology should grow up in New Haven, but it took the second generation to accomplish the fact. In that achievement, Professor Mendel has taken the lead. It is interesting, I think, to appreciate that the study of the individual plant proteins, in a very quiet way, in Professor Chittenden's laboratory and the nearby agricultural experiment station of Dr. Osborne, was really the start of all this work which Professor Mendel has presented to-night. For many years the work of Dr. Osborne was very little known. Now studies of nutrition, such as this work of Mendel and Osborne, are coming to bear strongly on a very interesting group of diseases—the so-called deficiency diseases. It is wholesome for us to find out that there is in the nutritional problem of normal growth something more than the provision of the mere energy requirement of the growing organism; and that there is a warrant for the belief—both in human pathology and in the physiology of the growing organism—that after all the instinct of the human race is going to be justified in the long run, and that we shall never be nourished on highly purified food products. For that outlook we have to thank Professor Mendel.

Dr. Welch: I should like to emphasize the fundamental importance of this work. The question of growth and what determines growth is of course at the bottom of not only physiological, but also of pathological, problems. I have felt that we never shall have an insight into the problems of pathological growth until the physiologists have given us a sound basis for the understanding of normal growth. Take, for instance, the most important of all pathological growths—cancer. In the last analysis, I am pretty well convinced that that is a question of an understanding of the factors concerned in growth. Take such work as Miss Maud Slye is doing now at the University of Chicago, where she has strains of mice with known pedigrees. In some strains there is no cancer, in others a certain percentage, and in still others something approaching 50-60 per cent developed cancer. She does not hestitate to speak of cancer as a mode of growth manifested as a hereditary phenomenon in some 50 per cent of the offspring of certain mice. What are the factors? Do they relate to what Dr. Mendel has spoken of as the inherited internal cellular factors, or do they relate to conditions around the cell—the environment? The former has been the usual idea. It is by no means certain that the wonderful capacity of cancer cells for almost indefinite growth does depend upon something inherent in the cell. I do not propose to attempt to develop the subject, except to thank Dr. Mendel for coming here and telling us of the results of this very important work, and to express the appreciation which I am sure all medical men and all pathologists feel for work of such a fundamental character.

Perhaps Dr. Winternitz will tell us something of the experiments he has recently been carrying on with chickens.

Dr. Winternitz: The few experiments that Mrs. Winternitz has stimulated me to undertake have had more to do with maintenance than with growth. Dr. Goetsch succeeded in causing rats to mature much more rapidly and to bear much larger litters than normal by feeding hypophysis. We thought the gland might have a similar effect on chickens. The experiments were begun last spring and have been encouraging, inasmuch as the chickens born about the first of May and fed upon hypophysis developed about twice as rapidly as the controls and have been laying eggs regularly all winter. The controls began laying when they were between nine and ten months old. The animals were given a minute quantity of whole desiccated hypophysis. One ounce, I think, has been given to 12 chickens over a period of six months. They were much larger than the normal chickens for a long time. At present they are only slightly larger and exhibit no abnormalities.

Our experiments are in exact contradiction to some recently reported from the University of California by Dr. Wilson. When fed with fresh hypophysis her chickens developed much less rapidly. Their bones were fragile and the animals remained infantile in type.

MARCH 15, 1915.

1. **Observations on Cardiac Dyspnea.** (Abstract.) DR. F. W. PEABODY, Boston, Mass.

In cases of pure cardiac disease with decompensation, the dyspnea may be associated with a transient acidosis. In cardio-renal disease the acidosis is a more permanent feature. In neither type of case, however, does the determination of the alveolar carbon dioxid tension give evidence of a high degree of acidosis, and it is difficult to decide in how far the acidosis is a factor in producing the dyspnea. Experiments have been performed in which subjects rebreathe their expired air, so that the inspired air contains a continually increasing concentration of carbon dioxid. Normal subjects and cardiac or cardio-renal patients who have no acidosis react in approximately the same way to this added stimulus. Decompensated cases, on the other hand, with acidosis, are more sensitive, and become dyspneic with a much lower concentration of carbon dioxid. They would certainly be in like manner more easily affected by carbon dioxid or other acids produced in the body itself than are persons whose blood is normal. Thus the acidosis is at least one factor in the cause of the dyspnea.

2. **The Factors of Coagulation in Experimental Aplastic Anæmia.** (Abstract.) DR. S. H. HURWITZ, Boston, Mass.

In the course of a study on the factors of coagulation in a case of aplastic anæmia we were impressed with the analogy existing between the symptom-complex in this disease and that observed by Selling in three cases of benzol poisoning. Observations on the blood of our patient disclosed changes not only in the formed elements but also in the circulating prothrombin.

This clinical finding stimulated us to apply the methods, supplied by Howell's investigations, to a study of the factors of coagulation in the experimental aplastic anæmia of benzol poisoning. It was with the hope of throwing some light upon the hemorrhagic features noted in this intoxication that our experiments were undertaken; but as the work progressed, it seemed to give some additional information concerning the relation of the bone-marrow to the origin of some of the factors studied.

Our observations have shown that the clinical symptoms of rabbits poisoned with benzol, so far as the hemorrhagic tendency is concerned, give only slight indication of the profound changes which this myeloid tissue poison produces in the blood of these animals. Although the latter did not, in the majority of instances, show marked signs of hemophilia, a study of the blood usually revealed striking changes both in the formed elements and in the prothrombin-content.

So far as the effect of benzol upon the formed elements is concerned, our experiments confirm the work of Selling and of Duke. Following the administration of benzol, there is a rapid disappearance of the white cells from the peripheral circulation. The red blood corpuscles are much less affected than the white cells and the blood-platelets. The latter, however, may remain at a high level at a time when the white cells have almost entirely disappeared from the circulation.

Besides the formed elements, we have followed the factors of coagulation in the majority of our animals. These studies showed that benzol exerts an important influence in reducing the circulating prothrombin and that this substance is dependent for its production, in part at least, upon bone-marrow activity. The two other factors of blood clotting—antithrombin and fibrinogen—were also followed. These were found to fluctuate but little from the normal.

Our results are in harmony with the recent proof that blood-plates contain prothrombin. They give additional evidence in support of the view that fluctuations in the amount of prothrombin may be produced by substances which affect the number of platelets, and that any toxin which produces a reduction in their number will simultaneously cause a diminution in the available prothrombin of the circulating blood. Our knowledge, moreover, of the origin of blood-platelets from the megakaryocytes of the bone-marrow emphasizes the importance of this tissue in maintaining the normal prothrombin equilibrium of the blood.

Although the marrow plays this important rôle in the elaboration of prothrombin, no definite parallelism could be established between the extent of bone-marrow injury, the number of blood-platelets and the relative amounts of prothrombin. This would suggest that it is not possible to create a dangerous prothrombin deficiency by a reduction in the number of blood-platelets alone and that some other tissue or tissues play some part in prothrombin formation.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

MARCH 8, 1915.

1. * **Two Physician-Economists: Sir William Petty, 1623-1687. Francois Quesnay, 1694-1774.** (Illustrated.) DR. JACOB H. HOLLANDER.

2. * **A Letter of Edward Jenner, Containing a Brief Account of His Discovery of Vaccination.** (Illustrated.) DR. CHARLES C. MCBRYDE, Washington, D. C.

THE LAENNEC.

MARCH 22, 1915.

1. **The Effect of Changes in Atmospheric Temperature Upon the Respiratory Tract.** DR. JAMES A. MILLER, New York City.

2. **The Rôle of Lymphocytes in Experimental Tuberculosis in Mice.** (Abstract.) DR. JAMES B. MURPHY, New York City.

This communication dealt with some interesting observations on the rôle of lymphocytes in tuberculosis experimentally produced in mice.

Dr. Murphy pointed out that the function of these cells had been underestimated, and indicated that the lymphocyte may be of primary rather than of subsidiary importance in resistance to infection with the tubercle bacillus.

Starting from the observations of Lewis and Margot that tuberculous animals develop large spleens, and that splenectomized animals infected three weeks after removal of the spleen survived the inoculation of tubercle bacilli longer than normal animals did, he sought an explanation of these facts.

With Dr. Lange he found that immediately after splenectomy the lymphocytes were decreased in number, whereas after 19 to 21 days the mice all showed a marked lymphocytosis. The author then confirmed Heineke's finding that the X-ray has an almost specific and immediate destructive action on the lymphoid system, and, in small doses, a minimal effect on other body cells.

Using splenectomy in some animals, the X-ray in others, a series of mice was available in which it was possible to note the influence exhibited by the lymphocyte in tuberculous infection, for in this series all gradations from a deficiency to an excess in the number of lymphocytes were present. The results of the inoculation of

* To appear later in the BULLETIN.

such a series of mice with tubercle bacilli were illustrated by charts. The essential findings were that in mice, that had been splenectomized and X-rayed before inoculation, the duration of life was shortest; whereas, mice that had been splenectomized 3½ weeks before inoculation survived infection for the longest period of time.

As a result of his experiments, and supported by clinical evidence, Dr. Murphy drew the conclusion that the lymphocyte is an important factor in the resistance of animals to tuberculosis.

DISCUSSION.

DR. WINTERNITZ: Dr. Murphy is to be heartily congratulated on his interesting studies. The power of ridding the body of a type of cells like the lymphocyte with the X-ray and the leucocyte with benzol has opened very broad fields for study.

Dr. Murphy has pointed out to-night the important rôle played by the lymphocyte in infectious granuloma. At a previous meeting of this Medical Society he indicated that the lymphocyte was equally important in the protection of the body against the invasion of tumors and I am sorry he has been unable to tell us more of this work to-night.

One confusing point has occurred to me concerning which I should like to question Dr. Murphy if I may? If the leucocyte is so potent in the protection of the body against tuberculosis, why does this infection lodge by preference, as it seems, in the lymphadenoid tissue?

DR. MURPHY: In answer to Dr. Winternitz's question on the involvement of the lymph glands in tuberculosis, I would say that we have, of course, considered this point. It will certainly require further investigation for a direct explanation. A number of theoretical suggestions might be brought forward as reasons for this frequent location of the infection. The lymph glands, as we know, act as filters for the materials getting into the lymph spaces. These are supposed to be common portals of entry for the tubercle bacilli. In the average individual these are taken care of, while in other individuals, either on account of a more virulent organism or a broken down resistance, the infection establishes itself. As a matter of fact, we know in general that tubercular infections of the lymph glands progress less rapidly than most of the other types.

DR. WINTERNITZ: Of course, the question of the spleen enters here. It is the abdominal organ most frequently affected by tuberculosis.

DR. MURPHY: In my experience the spleen is involved only in overwhelming infections. Here, as in lymph gland involvement, we can only theorize. The fact that the bone-marrow is involved often in certain pyogenic infections is not accepted as proof that the polymorphonuclear leucocyte has no function in the protection of the body against these types of organisms. The action of this cell is generally accepted. It seems to me that we have as strong, if not stronger, proof that the lymphocyte is just as important an agent of defense against the tubercle bacillus as is the polynuclear cell against certain other infections.

NOTES ON NEW BOOKS.

Chemical Pathology. By H. GIDEON WELLS, PH. D., M. D., Professor of Pathology in the University of Chicago and in Rush Medical College, Chicago; Director of the Otho S. A. Sprague Memorial Institute. Second edition, thoroughly revised. (*Philadelphia and London: W. B. Saunders Company, 1914.*)

The first edition of this volume has more than answered the purpose of the author; that is, it has furnished collateral reading in chemistry for the student of general pathology; it has correlated the chemical and physiological advances in medicine for the graduate; it has been a source of information to the investigator in biological chemistry and scientific medicine where these fields overlap; and, above all, it has answered as a guide to the original sources of our knowledge of these subjects.

To those who have been familiar with this book the appearance of the second edition will be greatly appreciated. The chemical study of biological problems has greatly increased in the past seven years, and the many substantial additions to the literature on the subject will be found classified and summarized in this volume.

The plan of the book is essentially that of the former one. Many portions have been largely or entirely rewritten, in accordance with the growing knowledge on the subject.

The careful selection of references throughout the volume makes a full bibliography of each subject readily accessible. The book remains unique in the English language and will continue to be a valuable aid to the student as well as to the investigator in scientific medicine.

Diseases of the Rectum and Colon and Their Surgical Treatment. By JEROME M. LYNCH, M. D. (*Philadelphia and New York: Lea & Febiger, 1914.*)

This volume is dedicated to the late Dr. J. P. Tuttle, with whom Dr. Lynch was associated and whose professorship in the New York Polyclinic Medical School he now occupies. Approximately the first half of the book is devoted to a consideration of the rectum and the anus; the latter half deals with the colon. The general plan of this volume is much like that of numerous other treatises upon the same subject. The author has, however, omitted the usual lengthy first chapter dealing with anatomy and physiology. This omission is decidedly an advantage, inasmuch as the facts contained in such chapters are easily accessible in any ordinary text-book on anatomy and add nothing of value to such clinical subjects as properly form the objective of a clinical text-book.

The first three chapters of Dr. Lynch's work are devoted to general subjects: Examination, Preparation of the Patient, and Anesthesia. Under the heading of Anesthesia a very sane valuation of local anesthetic methods is presented, the discussion being notably conservative and free from the rather extravagant advocacy of local anesthesia, which is just now rather popular. The most interesting feature of this particular chapter is the discussion of the author's method of extradural or sacral anesthesia. This consists in the introduction into the sacral canal of anesthetic fluids, which are designed to produce regional anesthesia. The idea is a very promising one and gives rise to the hope that its further development and practice will provide a valuable form of local anesthesia for this whole field of surgery. One is forced to regret, however, that the description of the technique employed is not entirely clear and there is not a sufficient volume of successful cases recorded to convince one, as yet, of its practical success.

Following the first three chapters the usual rectal diseases are given in order and the text is well supported by numerous illustrations. Many of the author's cases are of great interest, particularly those described under the heading of Malformation. The diseases of the colon are also handled in the same general manner and there are a number of excellent colored plates illustrating proctoscopic findings. The subject of cancer, which, of course, is one of paramount importance, receives ample consideration, much of the unnecessary and commonplace being omitted. In this chapter the author describes the blocking of the sympathetic

nervous system at the pelvic brim to reduce the shock in radical operations. There is an excellent illustration of a dissection of the lower abdominal and sacral sympathetic in connection with this phase of the operative procedure.

Finally, there are chapters on the use of serums and vaccines and also of X-ray examinations of the intestine. The book as a whole is readable and evidently is based upon a wide practical experience in this field of surgery. The illustrations, as before noted, are numerous and of good quality, and there is a comprehensive index. The technical perfection of the work is somewhat impaired by lack of careful proof-reading, as is instanced in the chapter on cancer, in which several sentences are made to read quite differently from what is the obvious intention. As a whole, however, the book is decidedly better, both as a practical aid and as a scientific study of this subject, than any of the other treatises of similar character which have appeared within the last few years.

Cystoscopy and Urethroscopy. By LEWIS and MARK. Cloth, $4.50. (*Philadelphia: Blakiston & Co., 1915.*)

The first portion of the book is devoted to a historical review of the development of cystoscopy and the various types of cystoscopes. A detailed description of the instruments and the technique of cystoscopy occupies a considerable portion of the volume. The development of urethroscopy is reviewed and there is a more or less detailed description of the different lesions which are to be found in the various portions of the urethra, together with rather good illustrations. Probably the most valuable portion of the volume is the chapter by Braasch in which he gives a concise, clear description of the changes in the pelvis in various kidney lesions, together with pyelogram illustrations.

The book contains many practical points which will be found useful for students. J. T. G.

John Shaw Billings: A Memoir. By FIELDING H. GARRISON, M. D. Illustrated. (*New York: G. P. Putnam's Sons, 1915.*)

The subject of this memoir possessed a commanding physical and mental personality which compelled respect and attention at all times. Born in Indiana in 1838 in the conditions of pioneer life and early thrown upon his own resources, by indomitable courage and force of character he gained, largely by his own exertions, a college training at Miami University, and medical training at the Ohio Medical College, two institutions, neither of which had then or now have a high standard of scholarship. Their work, however, was supplemented by the initiative and force of character of the diligent student, who learned thoroughly what to study and how to study. He entered the United States Army Medical Corps as a contract surgeon in the autumn of 1861 and was appointed lieutenant and acting surgeon in April, 1862. For more than two years he saw active service as an operating surgeon and in charge of army hospitals, mostly at the front in the Civil War. He shared in the arduous work at Gettysburg, Chancellorsville, in the battles of the Wilderness and before Petersburg. In 1864, however, because of his known and proved ability as a medical statistician and student of medicine, he was ordered to Washington to engage in special duties in the surgeon general's office, and there remained almost continuously until he was retired at his own request from the service in 1895. In Washington he became known as a sanitarian, an expert in vital statistics, an authority on ventilation, hospital construction, organization and medical education, a bibliographer and librarian, the creator of the most extensive medical library in the world and head of the Army Medical Museum. After his retirement from the army medical corps he became professor of hygiene in the University of Pennsylvania, but not for long. He was soon called to New York to take charge of the combined Tilden, Astor and Lenox Libraries which had become the New York Public Library and remained there until his death in 1913, after 17 years of service.

During this period of more than 50 years his wonderful mental activity is shown by his record of army service and by his bibliography which presents 171 titles of books and elaborate papers. He possessed the faculty of accomplishing his work rapidly with a maximum of results and a minimum of friction and lost motion. To the readers of the BULLETIN probably the chapter on his connection with the plan and building of The Johns Hopkins Hospital will make an especial appeal. Although Dr. Garrison has not added much to this chapter which was not already known to a few persons, he has brought out most interestingly the fact that Dr. Billings had preponderant influence not only in the adoption of the building plans, but also in shaping the organization of the different departments and in the selection of the heads of them like Welch, Osler, Halsted and others.

Dr. Garrison has written the memoir in a sympathetic spirit and has given interesting glimpses of Billings' character by extracts from his letters and note-books. He is thus shown as an affectionate husband, a fond father, an earnest student, a public-spirited officer of the government, cheerfully doing extra and uncompensated service in the census, in vital statistics, in marine hospital reorganization and in public duties at home and abroad. It was a busy, active and productive life. He was clearly the most forceful personality which the army medical corps has produced. His story is most interesting and inspiring. H.

A Laboratory Manual and Text-Book of Embryology. By CHARLES W. PRENTISS, A. M., PH. D., Professor of Microscopic Anatomy in the Northwestern University Medical School, Chicago. Octavo, of 400 pages, with 368 illustrations, many of them in colors. Cloth, $3.75. (*Philadelphia and London: W. B. Saunders Company, 1915.*)

Primarily a brief text-book of human embryology, in that sense it is based largely on the Manual of Human Embryology of Keibel and Mall. Dr. Prentiss has made his book practicable as a laboratory guide for medical students by basing the account of the segmentation stages on the amphioxus and frog's eggs; the development of the primitive embryo on the chick; and the general organology on various dissections and sections of pig embryos which represent the author's own experience. Thus he uses comparative anatomy on the basis that it gives available laboratory material, which he has welded together and related to human embryology. The author has drawn largely from the literature and wisely avoids repeating long literature lists which are covered by the Keibel-Mall manual. Of the 368 illustrations approximately one-third are new drawings. About sixty of the new drawings are of dissections and semi-diagrammatic reconstructions, of which those on the chick in the third chapter may be mentioned as especially instructive.

The text gives a brief but clear account of embryology and emphasizes organology, which makes so valuable a foundation for anatomy for the medical student. Dr. Prentiss' manual can be recommended as meeting a real need of the medical student in that it will give him a valuable introduction to the subject of human embryology. F. R. S.

Nature and Nurture in Mental Development. By F. W. MOTT, M. D., F. R. S. Cloth, $1.50. (*New York: Paul B. Hoeber, 1915.*)

This small book of 137 pages is an amplification of three Chadwick Trust lectures delivered last year.

The subject is a very vast one, but the matter is arranged in a simple, concise and helpful way. An idea of the scope of the book may be readily seen when one finds such things considered as (a)

Mental Hygiene from a Physiological Standpoint, (b) Causes of Mental Deficiency, (c) The Raw Material of Character in Relation to Heredity, (d) Genius in Relation to Heredity, (e) Sex in Relation to Character, Crime and Insanity, (f) The Influence of Nutrition and The Influence of Education in Mental Development, (g) Sex and Education. The above are only a few of the interesting items dealt with, but no doubt they will be sufficient to stimulate those interested to inquire further.

Emphasis is laid on the rôle of the sex glands in development, and the author believes that the suppression of the normal physiological processes of reproduction and of the maternal instinct of women is one of the pressing problems of civilization.

Dr. Mott admits that there are a few individuals of very defective intelligence who may be looked upon as born criminals, but he disagrees with the views of Lombroso and tries to show how crime is much more a matter of opportunity and environment.

One is glad to see that such a firm attitude is taken in regard to the care of the feeble-minded, and it is pointed out how, so far as the community is concerned, the higher-grade imbecile is a grave danger. A strong plea is entered for the early segregation of all mentally defective children.

There are some statements in the book with which we cannot agree. To quote a single instance: "The deeper the dementia (loss of mind) the greater are the number of nerve cells and fibers destroyed or undergoing decay and destruction" (page 24).

On the whole, however, the author's point of view is a very sound one, and the book can be heartily recommended.

D. K. H.

Nursing and Care of the Nervous and the Insane. By CHARLES K. MILLS, M. D. Third Edition, revised by the author, assisted by N. S. YAWGER, M. D. (*Philadelphia and London, J. B. Lippincott Company, 1915.*)

This little book by the well-known Philadelphia neurologist contains the substance of a course of lectures delivered to nurses. In the first chapter some of the personal qualities and qualifications of nurses who deal with nervous patients are touched on, and advice is given in regard to the nursing in cases of hysteria, epilepsy and similar conditions. In the second, third, and fourth chapters the use and technique of massage, hydrotherapy, and electricity are treated of; in the fifth are to be found more or less general rules to be followed in the care of insane patients.

The book is somewhat narrow in its scope, and cannot be particularly recommended.

Dissection Methods and Guides. By DAVID GREGG METHENY, M. D., etc. Cloth, $1.25. (*Philadelphia: W. B. Saunders Company, 1914.*)

This small book is an addition to the list (already large) of laboratory manuals which are designed to guide the student in the preparation of the various regions of the human cadaver, in order that the study of their component structures may be facilitated and undue mutilation be avoided. It is a compact and well-printed volume of 131 pages, in which the work of dissection is systematically laid out, the surface incisions being indicated by means of twelve simple illustrations. The outline has been planned so that work may be started with equal advantage on any part of the body. One good point is the absence of structural description, which makes necessary the consultation of standard text-books and atlases of anatomy; indeed, the author states that his guide is "designed for use in conjunction with a text-book, but it is not to supplant it in any way."

The practice of employing the old nomenclature in the text and of relegating the B. N. A. to brackets is a reversal of that usually followed, and is to be deplored, as tending to push unduly into the future the universal adoption of a single system of terminology.

Though it participates in the defects inseparable from all such guides, the book supplies a fairly good outline of some of the procedures to be followed in acquiring a knowledge of the morphology of the human body.

C. C. M.

Development and Anatomy of the Nasal Accessory Sinuses in Man. By W. B. DAVIS. Cloth, $3.50. (*Philadelphia: W. B. Saunders Company, 1914.*)

We must apologize to the author and the publishers for the long delay in reviewing this admirable book. A vast amount of painstaking work has been done by the author in collecting and preparing such a fund of material, in making measurements, noting anomalies, and describing other points of interest in the 290 anatomical specimens upon which the observations in the book are based.

The internist as well as the specialist should read this book, or at least study the series of beautiful drawings made by Miss Peters. To the teachers, especially, this book is warmly recommended. If the series of drawings are removed and properly grouped, they demonstrate very closely the various stages of development of all of the accessory sinuses and the relation of each of these sinuses to all the important surrounding structures. From a careful study of these can be obtained a better understanding of the various anomalies which are frequently encountered in clinical work.

In the laryngological dispensary of The Johns Hopkins Hospital these drawings, together with the appropriate legends, have been grouped and placed on the walls, so that the students and physicians may constantly refer to them.

The Interpretation of Dreams. By PROF. SIGMUND FREUD. Authorized translation of third edition, with introduction by A. A. BRILL. Cloth, $4.00. (*New York: The Macmillan Company, 1913.*)

Some idea of the increase of interest in the study of the psychoneuroses may be gleaned from the fact that whereas nine years elapsed between the first and second editions of this book only a little more than a year has gone by before the need for the third and present edition has arisen.

Since the appearance of the first edition the author's experience has induced him to lay even more weight on the significance of symbolism in dreams and consequently a number of foot-notes have now been added and numerous insertions have been made in the text.

In discussing Freud's work, a very common criticism is that little value should be placed on dreams, which are the product of psychoneurotic or diseased minds, and no doubt at the start it is well to emphasize the fact that Freud has forestalled the above objection by using his own dreams as examples of the points which he wishes to elucidate.

In Chapter I the scientific literature on the problems of the dream is fully and convincingly discussed and the great diversity of the views expressed in regard to the importance and non-importance of dreams is clearly put forth.

Freud believes that it may be taken as an indisputable fact that all the material composing the content of the dream has originated in experience, "but the connection has frequently to be carefully sought." He believes that the dream is an occurrence of our own psychic activity and that it thinks, especially in visual pictures, but also in auditory and other special sense impressions.

In the farther chapters of this interesing book Freud attempts to prove his assertions. With numerous striking examples he shows how a dream represents a wish as fulfilled and asserts that such is a universal and not merely an accidental characteristic. He frankly admits that superficially many dreams may seem to have a painful content, but that this is simply due to the fact that people do not differentiate between the manifest and latent content.

Upon analysis painful and fearful dreams may also be discovered as wish-fulfillments. There are many points and statements in the book that, with all due respect to the enormous experience and ingenuity of the author, one would hesitate to accept unreservedly, but these do not especially detract from the stimulating character of the book.

Diseases of the Skin. By FRANK CROZER KNOWLES, M. D. With 199 illustrations and 14 plates. (*Philadelphia: Lea & Febiger, 1914.*)

This volume compares favorably with other text-books of its class, but shows no material difference. There are the usual chapters on anatomy, physiology, general symptomatology diagnosis and treatment.

Diseases of the mucous membranes and the discussion of the eruptive fevers are dealt with in separate chapters.

The various methods of treatment from which the author himself has had the most satisfactory results are given and much profit can be obtained from reading these sections. In addition, the special and more recent remedies, such as vaccines, radium, the various electric appliances, refrigeration, etc., are dealt with. In an appendix are added numerous adjuvants, which are often found useful in dealing with cases of skin disease.

The descriptions of the various eruptions are clear and sufficiently complete; the points in differential diagnosis are well made. The various tests for syphilis and tuberculosis are outlined.

The illustrations, though numerous and well selected, have not been reproduced well; they are lacking in clearness and definition.

Morris' Human Anatomy. Edited by C. M. JACKSON, M. S., M. D. Fifth edition. $6 net. (*Philadelphia: P. Blakiston's Son & Co., 1914.*)

The book as a whole differs but little from its immediate predecessors, although reforms already initiated in the fourth edition have been extended. Small print for matters of general interest is more used. This not only facilitates reading, but it has also permitted the editor to enlarge the scope of the work and to insert many additional illustrations without making it cumbersome by adding to its bulk. The B. N. A. system of nomenclature is more generally employed than in the former edition. Several new departures have been made, as, for example, the insertion at the end of most of the sections of important references to the literature on the subject, so that the student can look up easily detailed information on topics which have interested him. It is to be hoped that in the next edition still more references of this sort will be given, particularly on the side of comparative anatomy. The insertion of illustrations of microscopic preparations leads to a valuable correlation of the gross findings with microscopic structure. A tendency is also evident, in some places, to lay increasing stress upon the functional rather than upon the purely morphological aspect of the subjects treated.

Many of the sections into which the book is divided have been written by authors who did not participate in the fourth edition. These sections have been much more changed than those revised by the same authors. The change is noticeable in the general scientific attitude, and in the point of view, rather than in the details of description, which must necessarily remain about the same. Professors Gunn, Huber, Jacobson, Morris and Sabin have withdrawn and Professors Clark, Jackson, Jones, Morley, Senior and Waterston have taken their places. The new work on the relative growth of the different parts of the body and on cytomorphosis has been incorporated in the section on morphogenesis The recent advances in our knowledge of the growth of lymphatics are also discussed. It is to be regretted that the advances which have lately been made by comparative neurologists in the interpretation of the plan of architecture of the human central nervous system have not been mentioned in detail. The section dealing with the digestive system has almost doubled in size. Space has been devoted to the discussion of the teeth (not given in the old edition), and the facts brought to light by recent experimentation with Roentgen rays relative to the form and position of the stomach and other viscera have been stated. Finally, the clinical and topographical anatomy has been strengthened by the insertion of many figures from X-ray photographs and by reference to operative procedures on the hypophysis and other structures.

E. V. C.

Text-Book of Surgical Operations for Physicians and Students. Illustrated by Clinical Observations. By PROF. FEDOR KRAUSE, Privy Medical Councillor, Directing Physician, Augusta Hospital, Berlin. In association with EMIL HEYMANN, M. D., Chief Physician, Augusta Hospital. Translated into English and edited for American readers by ALBERT EHRENFRIED, A. B., M. D., F. A. C. S. Assistant Visiting Surgeon, Boston City Hospital, etc. In six volumes. Vol. I. Cloth, $6.00. (*New York: Rebman Company, 1915.*)

The translator in his preface says that the book is primarily a text-book of operative surgery. It deals with the subject entirely from the personal viewpoint of its distinguished author, except where the translator has modified the text to suit American conditions. It approaches its subject in a novel way by the presentation and discussion of actual cases, which are carefully followed from the beginning through the operative treatment, to the end result.

The 260 pages are divided into 12 chapters. General surgical technic is considered in the first four. In the remaining chapters the surgery of the head is taken up as follows: Wounds of the head; extirpation of tumors in tissues of the face; plastic operations on the face, and special plastic procedures; the eye and orbit; the ear; the nose and accessory sinuses; the trifacial nerve. The appearance of the book is very inviting, with its attractive cover, thick paper, good print, wide margins, and graphic illustrations.

Judging from the contents of the first volume, one might be inclined to think that there would be more volumes than the amount of text justifies. In other words, if the same material were published in three, or possibly two, volumes, without any diminution in its value, it would reach a very much larger number of students and working surgeons, than in its present elaborate form.

J. S. D.

BOOKS RECEIVED.

Reducing Weight Comfortably: The Dietetic Treatment of Obesity. By Prof. Gustav Gaertner, M. D. Authorized translation in English. 1914. 12°. 313 pages. J. B. Lippincott Company, Philadelphia and London.

The Heart in Early Life. By G. A. Sutherland, M. D., F. R. C. P. 1914. 12°. 211 pages. Henry Frowde, London; Hodder & Stoughton, London; Oxford University Press, New York.

National Association for the Study of Pellagra. Transactions of the Second Triennial Meeting at Columbia, S. C., October 3 and 4, 1912. 1914. 8°. 409 pages. The R. L. Bryan Company, Columbia, S. C.

Clinical Society of the University of Michigan. Transactions, October, 1913–October, 1914. Vol. V. Edited by the Secretary-Treasurer. 1914. 8°. 175 pages. Ann Arbor, Mich.

Mechano-Therapeutics in General Practice. By G. de Swietochowski, M. D., M. R. C. S. With 31 illustrations. 1914. 12°. 141 pages. Paul B. Hoeber, New York.

Child Training as an Exact Science. A Treatise Based upon the Principles of Modern Psychology, Normal and Abnormal. By George W. Jacoby, M. D. With illustrations. 1914. 12°. 384 pages. Funk & Wagnalls Company, New York and London.

Acute General Miliary Tuberculosis. By Professor Dr. G. Cornet. Translated by F. S. Tinker, B. A., M. B., B. C., M. R. C. S., L. R. C. P. 1914. 8°. 107 pages. Paul B. Hoeber, New York.

A Text-Book for Midwives. By John S. Fairbairn, M. A., B. M., B. Ch. (Oxon.), F. R. C. P. (London), F. R. C. S. (Eng.). With 3 plates and 104 illustrations, 5 in color. 1914. 8°. 317 pages. Henry Frowde, London; Hodder & Stoughton, London; Oxford University Press, New York.

Evolution of Sex in Plants. By John Merle Coulter. 1914. 12°. 140 pages. The University of Chicago Press, Chicago, Ill.

Royal College of Surgeons of England. Calendar. 1914. 8°. 400 pages. Taylor and Francis, London.

Report of the Surgeon General, U. S. Army, to the Secretary of War. 1914. 8°. 306 pages. Government Printing Office, Washington.

Ohio State Board of Health. Twenty-eighth Annual Report of the State Board of Health of the State of Ohio. For the year ending December 31, 1913. 1914. 8°. 899 pages. Columbus, Ohio.

Carcinoma of the Thyroid in the Salmonoid Fishes. An Investigation and Experimental Study Conducted Jointly by the Gratwick Laboratory of the State Institute for the Study of Malignant Disease, Buffalo, N. Y., and the United States Bureau of Fisheries. By Harvey R. Gaylord, M. D., and Millard C. Marsh. With the collaboration of Frederick C. Busch, M. D., and Burton T. Simpson, M. D. Publications from State Institute for the Study of Malignant Disease. Serial No. 99. Issued April 22, 1914. 4°. Government Printing Office, Washington.

Text-Book of Massage and Remedial Gymnastics. By L. L. Despard. Second edition. 1914. 8°. 413 pages. Henry Frowde, London; Hodder & Stoughton, London; Oxford University Press, New York.

Therapeutics of the Circulation. By Sir Lauder Brunton, Bt., M. D., D. Sc., LL. D. (Edin.), LL. D. (Aberd.), F. R. C. P., F. R. S. Second edition. With illustrations. 1914. 16°. 536 pages. Paul B. Hoeber, New York.

Lead Poisoning: From the Industrial, Medical and Social Points of View. Lectures delivered at the Royal Institute of Public Health. By Sir Thomas Oliver, M. A., M. D., M. R. C. P. 1914. 12°. 294 pages. Paul B. Hoeber, New York.

Public Health Laboratory Work. By Henry R. Kenwood, M. B., F. R. S. Edin., D. P. H., F. C. S. Sixth edition, with illustrations. 1914. 8°. 418 pages. Paul B. Hoeber, New York.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W. Cattell, A. M., M. D. Vol. IV. Twenty-fourth series. 1914. 8°. 314 pages. J. B. Lippincott Company, Philadelphia and London.

Fever: Its Thermotaxis and Metabolism. By Isaac Ott, A. M., M. D. 1914. 12°. 166 pages. Paul B. Hoeber, New York.

Selected Addresses on Subjects Relating to Education, Biography, Travel, etc. By James Tyson, M. D., LL. D. [1914.] 12°. 366 pages. P. Blakiston's Son & Co., Philadelphia.

United States, Treasury Department. Annual Report of the Surgeon General of the Public Health Service of the United States. For the fiscal year 1914. 8°. 357 pages. Government Printing Office, Washington.

Laboratory Manual for the Detection of Poisons and Powerful Drugs. By Dr. Wilhelm Autenrieth. Authorized translation of the completely revised fourth German edition by William H. Warren, Ph. D. With 25 illustrations. [1914.] 8°. 320 pages. P. Blakiston's Son & Co., Philadelphia.

E. Merck's Annual Report of Recent Advances in Pharmaceutical Chemistry and Therapeutics. Vol. XXVII, 1913. 1914. 8°. 589 pages. E. Merck, Chemical Works, Darmstadt.

Interstate Commerce Commission. Twenty-eighth Annual Report (in two parts). Part I. December 1, 1914. 8°. 178 pages Government Printing Office, Washington.

Medical Diagnosis. By Arthur Latham, M. A., M. D. (Oxon.), F. R. C. P. (Lond.), and James Torrens, M. B., B. S. (Lond.), M. R. C. P. (Lond.). With 74 illustrations; 19 in color. 1915. 8°. 641 pages. Macmillan Company, New York.

A Handbook of Fevers. By J. Campbell McClure, M. D. (Glasgow). 1914. 8°. 470 pages. Paul B. Hoeber, New York.

Der Starrkrampf, seine Entstehung und Behandlung. Von Prof. Dr. Ferdinand Blumenthal. 1914. 12°. 79 Seiten. Urban & Schwarzenberg, Berlin u. Wien.

Praktikum der Chirurgie. Von Dr. O. Nordmann. I Teil. Allgemeine Chirurgie. Mit 90 teils farbigen Abbildungen. 1915. 8°. 216 Seiten. Urban & Schwarzenberg, Berlin-Wien.

Seuchenentstehung und Seuchenbekämpfung. Von Prof. Dr. F. Neufeld. Mit 24 Abbildungen. 1914. 12°. 204 Seiten. Urban & Schwarzenberg, Berlin-Wien.

Augenverletzungen im Kriege und ihre Behandlung. Mit einem Abriss über die Diagnose und Behandlung des Trachoms. Mit 46 Abbildungen. 1914. 12°. 96 Seiten. Urban & Schwarzenberg, Berlin-Wien.

Text-Book of Surgical Operations. By Prof. Fedor Krause, in association with Emil Heymann, M. D. Translated into English and edited for American readers by Albert Ehrenfried, A. B., M. D., F. A. C. S. In six volumes. Vol. I. With 55 plates having 233 illustrations in two or more colors and 61 figures in the text. 1915. 4°. 267 pages. Rebman Company, New York.

The National Association for the Study and Prevention of Tuberculosis. Transactions of the Tenth Annual Meeting, Washington, D. C., May 7-8, 1914. 8°. 448 pages. Wm. F. Fell Company, Philadelphia.

Congress of American Physicians and Surgeons. Transactions of the Congress of American Physicians and Surgeons. Ninth triennial session, held at Washington, D. C., May 6 and 7, 1913. 8°. 104 pages. New Haven, Conn.

American Surgical Association. Transactions of the American Surgical Association. Vol. XXXII. Edited by Archibald MacLaren, M. D. 1914. 8°. 713 pages. Philadelphia.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $2.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.